'ACID' PROSTATE PHOSPHATASE

AND

PRODUCTION OF TESTIS HORMONE IN MAN

especially in Relation
to Treatment with Chorionic Gonadotropin

BY

PER FROM HANSEN

With a Danish Summary

EJNAR MUNKSGAARD
COPENHAGEN 1949

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J. ENGELBRETH-HOLM,
h. a. dec.

ON COMMISSION TO EJNAR MUNKSGAARD
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To my Mother

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PREFACE

In solving the prize question in theoretical medicine for the year 1944 at the University of Copenhagen I conceived the idea of the present work. Professor Knud Sand, M. D., has taken a never failing interest in my examinations from the outset, and procured the best possible conditions for my work with the biochemical analyses, which have all been carried out at the Biochemical Department of the Institute of Forensic Medicine of the University of Copenhagen; the comprehensive biochemical knowledge of the chief of this department, Frank Lundquist, Ph. D., proved very useful to me.

I am particularly indebted to Professor Eggert Møller, M. D., who placed the Medical Outpatients' Department of the "Rigshospitalet" (the University Hospital of Copenhagen) at my disposal for the examinations, allowed me to examine the patients and endeavoured to facilitate the work for me in every way. All the examinations and treatments of the patients took place at this department, and most of the patients included in my series of cases were seeking medical advice there. Professor Preben Plum, M. D., the Department of Diseases of Children, the "Rigshospitalet", and Professor Erik Warburg, M. D., Medical Department B of the same hospital, have also most willingly placed their patients at my disposal.

The hormone preparations used were kindly given to me by "Løvens kemiske Fabrik" (Leo Pharmaceutical Products), and the Hormone-Biological Department of this institution, chief Mogens Tønnesen, Phar. D., kindly undertook most of the analyses for hormones in urine. The rest of the analyses were made

at the Hormone Department of the State Serum Institute, chief of the department Christian Hamburger, M. D..

In carrying out the statistical analyses Dr. N. K. Jerne has been of great assistance to me.

All the patients have been examined by me personally, and I have made all the analyses for phosphatase, creatinine and fructose. The photometric measurement have, however, been made by my wife, Dr. Inge From Hansen; in various other ways, too, my wife has her great share in the preparation of the work. In the course of numerous discussions of the problems that arose as a result of the examinations her sense of criticism and inspiring encouragement proved to be of invaluable advantage.

The first half of the book was translated by Axel Andersen, Sworn Translator and Interpreter, who has also assisted me in adapting the rest of the book in English.

I have received financial support from the Foundation of "Løvens kemiske Fabrik" to carry out the work.

I wish to express my gratitude for good assistance to all those mentioned above and to others who have helped me.

Copenhagen, October 21st, 1949.

Per From Hansen.

CONTENTS

INTRODUCTION AND SCOPE 15

Chapter I

HISTORICAL SURVEY OF PUBLICATIONS ON ACID PROSTATE PHOSPHATASE 19
Discovery of Acid Urine Phosphatase 19
Demonstration of the Seat of Formation of Acid Urine Phosphatase in Man 19
The Formation of Prostate Phosphatase is shown to be a Male Secondary Sex Character 20
Examinations of the Influence of Castration and Sex Hormones on Patients with Careinoma of the Prostate 21
Function of Prostate Phosphatase 21

Chapter II

NORMAL ANATOMY AND HISTOLOGY OF THE PROSTATE 23
Macroscopically 23
Histologically 23

Chapter III

INFLUENCE OF HORMONES ON THE PROSTATIC TISSUE 26
Androgens 26
Oestrogens 27
Mutual Effect of Androgens and Oestrogens 28
The Pituitary and the Prostate. Gonadotropin and the Prostate 28
Suprarenal Cortex and the Prostate 29
Desoxycorticosterone Acetate 29
The Prostate and the Vesicular Glands 30

Chapter IV

SECRETION OF THE PROSTATE 31
Experiments in Dogs 31
Intensity of Secretion in Man 32
Composition of the Normal Prostatic Secretion in Man 32

Chapter V

BIOCHEMICAL PROPERTIES OF PROSTATE PHOSPHATASE 33
Division of the Phosphatases 33
Classification and Chemical Properties of Prostate Phosphatase 33
Dependence of the Activity on pH 34
Dependence of the Stability on pH 34
Keeping Qualities 34
Inhibiting Substances 34

Chapter VI

CONTENT OF ACID PHOSPHATASE IN THE URINE 36
Sexual Stimulation and the Passing of Prostatic Secretion into the Urine 36

Chapter VII

THE EJACULATE IN MAN 38
Successive Composition of the Ejaculate 38
Concentration of Phosphatase in Ejaculates of Normal Individuals and of Infertile and Subfertile Individuals 39
Proportion of Prostatic Secretion in the Ejaculate 41
Content of Prostatic Secretion in Semen after Repeated Ejaculations 42
Previous Examinations 42
Writer's Examinations 43
Influence of Sex Hormones on the Ejaculate 44
Phosphatase Concentration of Ejaculate and Prostatic Secretion in Prostatitis 45
Proportion of Vesicular Secretion in the Ejaculate 46

Chapter VIII

PREVIOUS EXAMINATIONS OF THE CONNECTION BETWEEN HYPANDROGENIC CONDITIONS AND THE PRESENCE OF VARYING SUBSTANCES (EXCLUDING PHOSPHATASE) IN THE EJACULATE 47

Chapter IX

PREVIOUS EXAMINATIONS OF THE PRODUCTION OF PHOSPHATASE IN HYPANDROGENIC CONDITIONS 48

Chapter X

WRITER'S EXAMINATIONS OF THE CONCENTRATION OF PHOSPHATASE IN EXPRESSED PROSTATIC SECRETION 50
Introduction 50
Technique of the Methods of Examinations used in the present Work 50
Determination of the Concentration of acid Phosphatase in expressed Prostatic Secretion 51
Determination of the Concentration of Phosphatase in Ejaculate 54
Accuracy of the Phosphatase Analysis 54
Determination of Admixture of Urine, if any, to the Prostatic Secretion 64
Determination of Admixture of Vesicular Secretion, if any 65
Measurement of the Volume of the Testes 72
Measurement of Dimensions of the Penis 72
Estimate of the Growth of Pubic Hair and the Degree of the other Accessory Growth of Hair 73
Estimation of the Size of the Prostate 74
Estimation of Appearance of the Expressed Secretion 74
Determination of the Excretion of Renal Hormones 74
Determination of the Development of the Carpal Bones 74

Chapter XI

CHOICE OF A CRITERION OF THE PRODUCTION OF PHOSPHATASE IN THE PROSTATE 76

Chapter XII

APPLICABILITY OF THE CONCENTRATION OF PHOSPHATASE AS AN INDICATOR OF THE PRODUCTION OF TESTIS HORMONE 80
The Specificity of the Production of Phosphatase 81
Influence of Testosterone 82
Influence of Chorionic Gonadotropin 90
Influence of Equine Gonadotropin 91
Influence of the extragonadal Androgen Production 92
Previous Investigators 92
Writer's Series 93
Influence of Thyroid Hormone 95
Influence of oestradiol monobenzoate 97
Conclusion 99
Sensitivity of the Prostate to Testosterone 99
Overlapping of the Concentrations of Phosphatase in Normal and hypandrogenic Individuals 100
Reproducibility. Examinations of spontaneous Variations of the Concentration of Phosphatase in Expressed Secretion on Repeated Expressions 100
Errors in the Determination 100
Admixtures of other Fluids 101
Urine 101
Secretions from Genital Glands other than Prostate 105
Variations in the Composition of the actual Prostatic Secretion ... 105
Unit of Measurement 110
Periods of Latency and Abatement of the Prostatic Secretion. Reversibility 111
Previous Examinations 111
Writer's Examinations 112
Conclusion 116

Chapter XIII

SERIES OF NORMAL CASES 118
Normal middle-aged Men 118
Normal Adolescents 125
Normal Individuals in the Senium 125
Previous Investigators 125
Writer's Series 126
Correlation between Concentration of Phosphatase and Age in Normal Individuals 128

Chapter XIV

HYPANDRY AND SEXUAL MATURITY. NOSOGRAPHIC CONSIDERATIONS 129
Hypandrogenic States 129
Diagnosing Pathological Hypandry 130
Androgen Production in Childhood 131
Retarded Development and Infantilism 132
Pubertas tarda 134
Eunuchoidism 135
Adiposogenital Dystrophy 135
Sexually mature Dwarfs 139
Testicular Hypoplasia 139

Chapter XV

WRITER'S EXAMINATIONS OF THE CORRELATION BETWEEN THE CONCENTRATION OF PHOSPHATASE AND THE OTHER SOMATIC SEX CHARACTERS IN HYPANDRY AND CERTAIN OTHER CONDITIONS 140
Composition of the Series 140
Hypandrogenic Boys and Men, not previously treated with Sex Hormones 147
Volume of Testes and Production of Phosphatase 156
Size of Penis and Production of Phosphatase 156
Pubic Hair and Production of Phosphatase 156
Terminal Hair and Production of Phosphatase 156
Appearance of Prostatic Secretion and Production of Phosphatase 157
Excretion of Androgens in Urine and Production of Phosphatase 158
Development of Carpus and Production of Phosphatase 159
Age and Production of Phosphatase 159
Hypandrogenic Boys and Men, previously treated with Sex Hormones 159
Correlation of Phosphatase Concentration to Age in Untreated and Treated Persons 161
Imbecile Boys during Puberty 161
Conclusion 161
Hypoplasia testis 163
Impotentia coeundi 165
Gynaecomastia 169
Previous Authors 169
Writer's Examinations 169

Chapter XVI

SEXUAL MATURATION AND ITS MECHANISM IN BOYS. PREVIOUS INVESTIGATIONS 171
Spontaneous Puberty 171
Early Onset and Rapid Course of Puberty 175
Delayed Onset of Puberty 176
Various Mechanisms of Sexual Maturation. Terminology 176

Chapter XVII

WRITER'S EXAMINATIONS OF THE DIFFFERENT FORMS OF PUBERTY BY MEANS OF THE PHOSPHATASE REACTION 179
Spontaneous Puberty in untreated Individuals 179
Sex Maturation caused by Chorionic Gonadotropin: Imitation of Puberty or Provoked Puberty 180
Surveys of the Series of Patients and Results 182
The Phosphatase Concentration before, during, and after the first Course of Chorionic Gonadotropin Injections 182
Conclusion 186
The Phosphatase Reaction in Patients with initially absent Production of Phosphatase 186
Review of the Series 190
The Difference in the Phosphatase Reaction between the Infantilism Group and the Patients suffering from Adiposogenital Dystrophy 191
The Phosphatase Production in repeated Courses of Chorionic Gonadotropin Injections 195
Imitation of Puberty after the first Course 195
Conclusion 197
Provoked Puberty after concluded Chorionic Gonadotropin Treatment 198
Combinations of Imitation of Puberty, provoked Puberty and spontaneous Puberty in the same Individual. Previously untreated and previously treated Patients 198
Concurrence of Imitation and Puberty 199
Concurrence of provoked and spontaneous Puberty 199

Chapter XVIII

RELATION BETWEEN TYPE OF PUBERTY AND DEGREE OF SEXUAL MATURITY ATTAINED 250
Conclusion 252

Chapter XIX

INFLUENCE OF CHORIONIC GONADOTROPIN TREATMENT ON THE POSPHATASE CONCENTRATION AND ON THE EXCRETION IN URINE OF GONADOTROPIC, ANDROGENIC AND OESTROGENIC SUBSTANCES 253
Previous Examinations of the renal Excretion of Hormones influenced by Chorionic Gonadotropin 253
Writer's Examinations 254
The Phosphatase Reaction and Gonadotropinuria 259
The Phosphatase Reaction and Androgenuria 261
The Phosphatase Reaction and Oestrogenuria 261

Chapter XX

LINES OF TREATMENT OF HYPANDROGENIC INDIVIDUALS WITH CHORIONIC GONADOTROPIN BASED ON THE PHOSPHATASE REACTION 263
Pituitary Hypofunction with Regard to the Production of Gonadotropin 263
Testicular Hypofunction with Regard to the Production of Androgen 264
Amount of the Spontaneous Gonadotropinuria and the Phosphatase Response to Chorionic Gonadotropin 264
Response to Chorionic Gonadotrópin as Prognostic Criterion 266
Therapeutical Indications 267
Adiposogenital Dystrophy 267
The Infantilism Group 268
SUMMARY IN ENGLISH 271
SUMMARY IN DANISH 289
CASE RECORDS 304
REFERENCES .....

INTRODUCTION AND SCOPE

The intensity of the production of an endocrine gland can be determined in two fundamentally different ways: the determination may either aim at the hormone itself or it may record the influence of the hormone on a physiological or biochemical organic function in the individual under examination.

The determination of the production of testis hormone is carried out by both methods. With regard to the former possibility it is, however, for the present possible only to use the excretion in the urine of the decomposition products of the hormone as a — certainly very indirect and rather unspecific — measure of the output of hormone. It may, however, be mentioned here that a method for the estimation of the concentration of androgens in the blood has been elaborated by T ö r n b l o m (1945). The other principle — the observation of the effect of the hormone on the organism in which it is produced — forms the basis of the clinical estimate of the production of any endocrine gland and of the effect of any hormonal therapy. A quantitative estimate of this requires determination of the hormonal effect on one or more of the functions of the organism which respond to hormones.

However, as far as the testis hormone is concerned, such an unambiguous biometric method is lacking (as already mentioned, the biometric estimation of the content of hormone in the urine comes under the principle first mentioned, and here it is the effect on the hormone-sensitive functions of another organism, the growth of the cock's comb or the prostate, which is registered). Sex characters such as the size and consistency of the testes, the ossification of the epiphyses, the height of the

individual and the length of the extremities are all rather unspecific. The degree and extent of the terminal growth of hair are more specific (though the share of the suprarenal glands has not ben elucidated) but are chiefly irreversible functions — like the ossification of the epiphyses — which will only slowly or incompletely register a fall in the output of testis hormone.

As generally known, the prostate is an organ which is very sensitive to androgens, and its function depends on a constant supply of androgens. Therefore, it seems reasonable to examine whether it is possible to use the prostate of a man as an organ of registration for his production of testis hormone. The size of the prostate is a less suitable clinical object for measuring and, as better criteria for the function of the prostate in man have been lacking so far, it is readily understood that the interest which human endocrinology has taken in the prostate is greatly outdistanced by the one which investigators dealing with animal subjects have taken in this organ; in the latter experiments the size, weight and microscopical conditions of the prostate have been used for more than one generation (Steinach, Sand, and others).

It has appeared that the normal male prostatic secretion contains the enzyme "acid" phosphatase in an exceedingly high concentration (Kutscher and Wolbergs, 1935 b) and further that the production of this phosphatase in the prostate of the rhesus is influenced by the androgenic hormones (Gutman and Gutman, 1939).

These two discoveries and the requirement described above are the motives of the present work, the main object of which was to attempt to find out whether the formation of the acid prostate phosphatase may be used as a measure of the production of testis hormone in man.

In the following the concentration of phosphatase in prostatic secretion obtained by digital massage is chosen as a criterion for the production of phosphatase by the prostate. It would possibly have been just as rational, or more so, to choose the formation of phosphatase per time unit as a criterion but, for reasons which will be

mentioned in the following, it has not been practicable to make use of this function.

The applicability of the production of phosphatase as a criterion for the output of testis hormone depends on the extent to which it complies with the conditions required of a biologic object for measuring, such as specificity (in this case with regard to testis hormone), reversibility, short latent and abating periods, reproducibility of the values and their suitable sensitivity to the adequate stimulus. These properties have been examined by following the production of phosphatase during and after a treatment with androgenic and other hormones; and the production of phosphatase has also been considered in relation to the age of the individual and to other manifestations of the androgen activity, such as the size of the testes, the measures of the penis, terminal growth of hair, development of the bones, and androgenuria.

Having thus acquired a knowledge of the response of the prostate to the production of testis hormone, it will be possible to follow the hormonal regulation at a still earlier stage: the prostate depends on the testes, the later depend on the pituitary or on administered gonadotropic hormone. The output of phosphatase during and after treatment with gonadotropin records the response of the testes to superior sexual hormone. Under certain conditions a comparison between the output of phosphatase before and after such stimulation will also afford information about the production of gonadotropin by the pituitary, as will be explained in one of the subsequent chapters.

It would be of particular interest to compare the results of such a gonadotropin test in boys suffering from so-called adiposogenital dystrophy with the result found in boys with various forms of inhibited development, as the investigations of recent years (see, for example, B r u c h, 1941) seem to show that there is no genital dystrophy in boys of the former type.

A material part of the investigations which will be reported in the following deal with the response of the prostate during and in particular after treatment with gonadotropin. In these examinations it has been attempted to elucidate the pathogenesis in a number of the disorders affecting the sex characters of boy and man; moreover, the object has been to extend the

knowledge of the processes of puberty and further to rationalize the treatment of male patients with gonadotropin. One of the necessary conditions in solving these problems is that the criterion chosen for the output of testis hormone, the production of phosphatase, has a short period of abatement, so that a fall in the output of testis hormone can be recorded without any distortion. Only then it will be possible to decide whether gonadotropin has had a lasting effect or only exerted a temporary stimulating effect in the case under examination.

Chapter I

HISTORICAL SURVEY OF PUBLICATIONS ON ACID PROSTATE PHOSPHATASE

The exploration of acid phophatase has in the course of time been directed towards five main subjects. An exposition on this basis — like the one given below — will only differ slightly from the chronological sequence of the examinations undertaken by previous authors.

1. **Discovery of Acid Urine Phosphatase.**

In 1925 Demuth demonstrated the presence of phosphatase with optimum activity at an acid reaction (pH about 5) in various fluids of the body, including the urine of both infants and adults. As only alkaline phophatases were known at that time, the discovery was met with some doubt but ten years later it was corroborated by Waldschmidt-Leitz and Nonnenbruch (1935) and Dmochowski and Assenhajm (1935). However, as early as in 1933 Dmochowski showed that urine phosphatase was greatly inhibited in the urine, so that the effect was multiplied by dilution or dialysis. As shown by Kutscher and Wolbergs in 1935 (*a*), this inhibition is due to the content of inorganic phosphate in the urine.

2. **Demonstration of the Seat of Formation of Acid Urine Phosphatase in Man.**

On the basis of the observation that, in particular in urine from the morning, there may occur incalculable rises of the phosphatase activity in adult males, but not in females and old males, Wolbergs considered the prostate an essential seat

of formation, and Kutscher and Wolbergs (1935 *b*) proved this right by demonstrating that tissue of the human prostate and ejaculated semen contain large quantities of acid phosphatase, and that this displays the same characteristics as the urine phosphatase in males.

The acid phosphatase in the urine of children, women, male castrates and men in the senium is serum phosphatase excreted through the kidneys (Waldschmidt-Leitz and Nonnenbruch, 1935), or it may possibly be phosphatase from the renal tissue itself (Dmochowski and Assenhajm, 1935).

Kutscher and Wolbergs' achievement directed the interest from the urine to the prostate and its acid phosphatase. As soon as in 1936 their observation was corroborated by Gutman, Sproul and Gutman who found large quantities of acid, but no alkaline, phosphatase both in normal and carcinomatous human prostatic tissue and in metastases from carcinoma of the prostate. Gutman and Gutman showed (1938 *b*) that acid phosphatase is also found in the caudal lobe of the prostate of the mature rhesus, which in contrast to man contains ample basic phosphatase in addition. But acid phosphatase is not produced to any appreciable degree in the prostate or in the other glands of the reproductive system of animals such as bulls, dogs, cats, rabbits, and rats. The preputial glands of the rat, which are strikingly rich in acid phosphatase, form an exception.

In 1938 (*a*) Gutman and Gutman found acid phosphatase in normal human serum, possibly derived from the liver or the spleen but not from erythrocytes or the prostate. In the same year (1938 *c*) they were able to demonstrate a considerable amount of acid phosphatase, which possessed the same properties as the prostate phosphatase, in the serum of patients suffering from metastases to the bones from carcinoma of the prostate.

3. **The Formation of Prostate Phosphatase is shown to be a Male Secondary Sex Character.**

In 1939 it was shown by Gutman and Gutman that in prepubertal monkeys, in which the prostate contains no phosphatases, it was possible to elicit a production of acid phosphatase to the same extent as is seen in the full-grown monkey, by

administration of testosterone propionate, which increased the growth of the glandular epithelium, whereas oestradiol monobenzoate, which influenced the fibromuscular elements in particular, was incapable of increasing the output of phosphatase.

In 1942 Scott and Huggins suggested to utilize the content of phosphatase in 24-hour urine as a measure of the production of testis hormone and, in 1945, it was shown by the writer that prepubertal males, or deficiently mature men, are lacking or have a decreased output of phosphatase in prostatic secretion obtained by digital massage, and that the output of phosphatase is started or accelerated under treatment with chorionic gonadotropin. In 1947 Engberg, Andersson, Sury and Raft found that cryptorchids have both a lowered phosphatase concentration in the ejaculate and a decreased excretion of andrin in the urine, and that there is a correlation between the phosphatase concentration and andrinuria in such patients.

4. **Examinations of the Influence of Castration and Sex Hormones on Patients with Carcinoma of the Prostate.**

It has been known for long that castration causes atrophy of the normal prostate, and it has now appeared that a similar regression takes place in malignant tissue of the prostate.

In 1941 Huggins, Stevens and Hodges published the results of castration in 21 cases of carcinoma of the prostate, most of them with metastases to the bones. Castration exerted a marked effect on the prostate, but also the metastases subsided with a tendency to healing, as demonstrated by X-rays, so that the neuralgic pain vanished and the general health improved considerably. In the same year (1941) Herbst had achieved a good remission by the administration of stilboestrol to a patient suffering from cancer of the prostate.

Further, Huggins and Hodges (1941) examined the influence exerted on the activity of acid phosphatase in serum both by castration and oestrogen therapy, both of which reduced the activity, and by treatment with androgens which exerted the reverse effect. These findings have been confirmed by numerous subsequent investigators.

5. **Function of Prostate Phosphatase.**

In 1946 and 1947 (*a*) Lundquist showed that the natural

substrate for prostate phosphatase in the ejaculate of man is phosphoryl choline which is produced by the vesicular glands (syn.: seminal vesicles *), and that the phosphoryl choline is decomposed very soon after the ejaculation.

*) The term vesicular glands is preferred here, as the function of the organ is secretory and not, as previously supposed, to contain the spermatozoa. The term: vesicular secretion is used in the following to designate the secretion of this organ.

Chapter II

NORMAL ANATOMY AND HISTOLOGY OF THE PROSTATE

The normal anatomy and histology of the prostate have been very thoroughly examined by R. A. Moore (1936 *a*, *b*) whose findings form the basis of the following brief description of the normal prostate in man.

Macroscopically the structure inside the capsule of the prostate can be divided into 4 groups: (1) the urethra with its evaginations, (2) the vas deferens with the ejaculatory duct, the prostatic utricle and possibly some of the vesicular glands, (3) the periurethral glands, and (4) the actual prostate gland.

The prostate can be further divided into anterior, posterior and median lobes and two lateral lobes, according to their situation in relation to the urethra and the vas deferens. Each lobe consists of many lobules; the borders between the lobules are not well-defined.

The normal volume of the prostate from birth to the beginning of puberty is found to be from 1 to 4 ml. Then it increases rapidly (in the course of about a year (Swyer, 1944) to 10 ml, and this volume is retained until about the fiftieth year of life. After this age the prostate may behave in one of two ways: It may undergo a gradual atrophy causing the volume to decease, or — more frequently — hypertrophic changes occur resulting in a great increase of volume, which persists until death. This tendency to either atrophy or hypertrophy is also seen in old dogs (Zuckerman and Mc Keown, 1938).

Histologically the prostate passes through considerable changes as the individual grows older. In the years from the

first to the tenth year of life the epithelium is a low cubical one, arranged in one or two layers. Apart from an increase of the number of acini, no changes are observed in the histological picture during this period. The lumina remain narrow, a few oval or round acini are, however, seen.

About the tenth year of life signs of incipient activity can be observed; the acini become round, the lumina increase in size, the glandular epithelial cells become more cylindric and now develop a distinct zone of cytoplasm between the nucleus and the lumen but do not to begin with discharge any secretion into the lumen. Between the twelfth and fourteenth years the above-mentioned rapid increase of the volume of the prostate occurs, which is caused almost exclusively by renewed development and ramification of the alveoli; moreover, numerous intra-alveolar papillae are seen, and the epithelial cells become capable of function.

In the third and fourth decades the appearance of the prostate remains fairly unchanged. The epithelial cells of the same prostate vary quite considerably both with regard to size and structure. The varying appearance of the cells of the same prostate seems to be due to different phases of the secretion. It is at any rate possible to classify the different forms of appearance of the cells in a (hypothetic) secretory cycle which shows transitions from low cubical to tall cylindric cells, the latter with a blurred luminal delimitation indicative of apocrine secretion. The cubical cells are supposed to be in a resting phase.

In the fifth and sixth decades presenile changes occur, manifesting themselves by an increasing inhomogeneity of the structure of the prostate. An increased growth of the cells occurs in the form of hyperplasia, pseudo-acinous formations and metaplasia, but also atrophic phenomena are seen, appearing as small obliterated acini in which the epithelium is flat and displays no signs of secretion. With advancing age the changes comprise an increasing number of acini, so that about the eightieth year half the number of alveoli have become obliterated and none of them show any signs of secretion. In most of the glands the hypertrophic processes will prevail, and only a small number display purely atrophic phenomena (see above).

The most characteristic signs of advancing age are as follows:

a) Between the fortieth and forty-fifth years the epithelial cells of the alveoli begin to assume different lengths;

b) between the forty-fifth and fiftieth years the lobular atrophy begins;

c) between the fiftieth and sixtieth years the glandular epithelium begins to lose its ability to secrete;

d) between the sixtieth and seventieth years atrophy of the unstriated musculature and an increase of the fibrous tissue of the stroma occur;

e) after the sixty-fifth year the corpora amylacea increase in size and number.

The prostates of castrates display atrophy of the papillae in the acini and low cells of the glandular epithelium, and present a histological picture closely resembling the one seen in the senile atrophic prostate.

Thorborg (1948) pointed out that the changes occurring in the prostate with advancing age exceed those observed in other organs, as the gland does not follow an "ordinary" growth curve from birth to death but displays a sudden development at puberty and characteristic changes in the senium; he also associated the senile changes with those taking place in the hormonal metabolism of the organism.

Chapter III

INFLUENCE OF HORMONES ON THE PROSTATIC TISSUE

Androgens.

The normal function of the prostate is determined by the presence of androgenic substance in the organism. As first shown by Hunter (1786), orchidectomy causes atrophy of the prostate.

A prostate of normal function is characterized histologically by a, mainly tall, cylindric epithelium in the large acini, with clear areas below the basal nuclei towards the lumen. In case of decreasing faculty for secretion caused by a reduced androgen stimulation the clear areas first disappear, later the tall cylindric epithelium becomes flattened (Huggins and Stevens, 1940, Burrill and Greene, 1940), the size of the nuclei is reduced and the diameter of the acini diminishes (Moore, Price and Gallagher, 1930). The last-named authors also found that it is possible histologically to demonstrate the effect even of small quantities of androgen on the ventral lobe of the prostate in rodents; this lobe is especially well-developed in these animals, and androgen was seen to prevent the regression of the prostatic tissue which normally occurs after castration. They consider this histological control the most sensitive test in mammals for the androgens and, using castrated rats as subjects, they are able to detect one-tenth of the dose of androgen required for complete restitution of the prostate.

In examinations of isolated tissue of the prostate Barrow and Huggins (1944) have shown that the androgenic hormones take part in the regulation of the oxidative phase of

the carbohydrate metabolism of the gland, which decreases after castration or in case of administration of oestrogen whereas the anaerobic phase remains uninfluenced.

In castrated albino rats the normal microscopic and macroscopic structures of the prostate can be re-established solely by means of testosterone propionate (Moore and Price, 1938).

Oestrogens.

The oestrogenic substances also exert a marked effect on the prostate. The principal rule is that small doses influence only the structures near the urethra and the seminal colliculus. The acini are influenced only by larger doses. In male mice and rats the oestrogens produce a reversible growth of the dorsocranial lobes of the prostate (syn.: coagulation glands) and metaplasia of their epithelium with cornification; further, proliferation of the dorsocaudal lobes and atrophy of the ventral portion of the prostate (Geissendörffer, 1940).

In dogs (De Jongh, 1935, De Jongh, Kok and van der Woerd, 1938) an increase of the fibromuscular tissue is produced in all the lobes, the dorsocranial lobes, however, being the most sensitive, and with larger doses the above-mentioned epithelial changes in the excretory ducts are seen as well. Neither these authors nor Huggins and Clark (1940) have been able to demonstrate changes in the epithelium of the acini following treatment of castrated dogs with oestrogen, except with very large doses (Huggins and Clark) which caused flattening of the cells of the glandular epithelium, even in case of simultaneous treatment with testosterone. However, Zuckerman and Groome (1938) have been able to influence the epithelium of the alveoli by means of oestrogen.

In treatment of the male rhesus with oestrogen the hypertrophy of the fibromuscular tissue prevails (Courrier and Gros, 1935, Zuckerman, 1936), in particular round the vagina masculina.

In male foetus from the eighth foetal month and in boys during the first two months of life there is metaplasia of the epithelium in the cranial lobe and the cranial portion of the anterior lobe (Aschoff, 1894, Schlacta, 1904). Halban (1904) supposed that this histological picture was due to a hormonal influence from the blood of the mother, a supposition

confirmed later by Sharpey-Schafer and Zuckerman (1941) who showed that the changes can be retained by administration of oestrogen.

Moore and McLellan (1938) have by operation of 5 men after 10 to 31 days' treatment with total doses of oestradiol monobenzoate varying from 15,000 to 140,000 I. B. U. found squamous metaplasia of the epithelium in the collecting tubules, and lymphocyte infiltration.

In repeated biopsies Hamilton, Heslin and Gilbert (1937) were unable to demonstrate any changes of the histological picture of the prostate in men after treatment for 26 days with oestrone in total doses varying from ⅔ to 2 mg.

With regard to the details to the effect of the oestrogen on the prostates of various animals, reference may be made to Thorborg's publication (1948).

Mutual Effect of Androgens and Oestrogens.

The effect of these two groups of hormones on the epithelium of the prostate in mice, rats and monkeys can be neutralized each by the other; the effect of daily injections of oestrone into the prostate of the rhesus monkey is thus neutralized by the sevenfold quantity by weight of testosterone propionate administered weekly, or by twenty times the quantity by weight injected every fortnight (Zuckerman, 1936). Similarly, larger quantities of oestrone are required for normal male mice than for castrated mice in order to produce the same oestrin effect.

In normal but not in castrated male mice De Jongh and van der Woerd (1937) managed to inhibit the oestrin effect by means of chorionic gonadotropin.

It has been ascertained by means of "biological titration" in castrated dogs (Huggins and Clark, 1940) that 0.1 mg of diethylstilboestrol as the lowest daily dose converts the constantly increasing secretion of the prostate which occurs with a daily administration of 10 mg of testosterone propionate into a constant secretion.

The Pituitary and the Prostate. Gonadotropin and the Prostate.

Hypophysectomy in dogs causes a marked atrophy of the prostatic epithelium, and the gland assumes a prepubertal appearance.

Constant administration of chorionic gonadotropin causes prostatic transplants in the anterior chamber of the eye of the rabbit to grow only to a certain extent; if then another preparation, e. g. equine gonadotropin, is chosen, the growth continues (Krichesky, Benjamin and Rosenberg, 1943). The same authors demonstrated the peculiar fact, that injection of gonadotropin produces a double-peaked growth curve, measured on an intra-ocular prostatic implant, so that the secondary growth does not begin until the treatment has been stopped.

Treatment of castrated animals with gonadotropin does not influence the prostate (Engle, 1939, Moore, Melchioma, Tolins and Rosenblum, 1937).

Suprarenal Cortex and the Prostate.

Under certain circumstances the suprarenal glands are capable of retaining a normal, though immature, prostatic picture (Price, 1936). This so-called "Price-effect" means that castration of immature male rats does not cause any direct atrophy of the prostate but that, on the contrary, the development of the gland continues until about the fortieth day of life, no matter how early the castration was performed, after which a regression sets in. This non-testicular stimulation is supposed to be due to the juvenile cortex of the suprarenal glands, more precisely the so-called X-zone (Howard, 1937), which subsides just about the fortieth day (Price, 1939). After adrenalectomy the Price-effect ceases (Burrill and Greene, 1939). Moreover, adrenocorticotropic hormone produces hypertrophy of the suprarenal glands and the prostate in immature castrated rats (Davidson and Moon, 1936) but not in animals which have been adrenalectomized as well (Davidson, 1937). Adrenalectomy exerts no influence on the prostate in uncastrated rats (Burrill and Greene, 1939). The observations mentioned here could not be corroborated by Gersh and Grollman (1939) who did not find the andromimetic effect after adrenalectomy to cease. Burrill and Greene have therefore resumed the subject (1940), illustrated it with renewed examinations, and insist on their findings.

Desoxycorticosterone Acetate.

This substance does not influence the ventral lobe of the prostate in castrated male rats (Greene and Burrill, 1940)

and guinea-pigs (Clausen, 1942) but slightly reduces the prostatic secretion in dogs (Huggins, Scott and Hodges, 1941). The substance is also denied any androgenic effect by Paschkis (1941), whilst Courrier and Bennetz (1943) maintain that it increases the weight of the prostate in castrated male rats if they are young.

The Prostate and the Vesicular Glands.

According to Moore and Price (1932) and Castillo and Pinto (1938), treatment with oestrone is capable of delaying the occurrence of the atrophy of the vesicular glands which follows castration; similarly, the growth of the prostate and the vesicular glands will increase in castrates who are being treated with testosterone propionate if oestrone is administered simultaneously. In young uncastrated male rats, too, oestrone is capable of increasing the weight of the vesicular glands. The smallest quantity of oestrogen which influences these glands is three times the one influencing the prostate (Moore and Gallagher, 1930).

According to Moore and Price (1938), the lowest dose of testosterone propionate by means of which a normal prostate can be produced in castrated rats is lower than the one producing normal vesicular glands; a normal histological picture of the latter can be obtained by means of doses varying from one-third to one-fourth of those required in order to attain a normal weight.

According to this, Nelson (1934 *a*) demonstrated that the vesicular glands in experimentally cryptorchid animals undergo castration changes, which fail to appear, or are only slight and occur later, in the prostate.

Chapter IV

SECRETION OF THE PROSTATE

Experiments in Dogs.

The secretion of the prostate in dogs is of a considerable size; under the influence of pilocarpine the gland may in a quarter of an hour produce an amount of secretion equal to its own weight, but otherwise there is no correlation between the weight of the prostate and the attainable volume of secretion in dogs of the same weight. These and other thorough examinations of the prostatic secretion in dogs have been made by Huggins, Masina, Eichelberger and Wharton, 1939, by means of a special surgical separation of the urine from the prostatic secretion. By means of this technique it appeared, among other things, (Pazos and Huggins, 1945) that inanition soon makes the secretion stop; in spite of continued complete inanition the secretion may, however, be re-established and of a well-preserved composition, even in castrated animals, when androgen is administered, or — in intact animals — under treatment with equine gonadotropin; the latter, however, is only active at the beginning of the period of inanition.

Further, the secretion is diminished, or ceases, after castration but can be re-established, though not always to the normal extent, by mans of testosterone propionate. Treatment of intact animals with oestrogen may cause the secretion to diminish already after the first 24 hours, and to cease after treatment for 10 days (Huggins and Clark, 1940).

The secretion of the prostate in dogs is under the nervous influence of the nervi hypogastrici and erigentes. Pilocarpine causes prolonged stimulation of the secretion, and the sub-

stance secreted is of a composition different from the one produced at rest (Berg, Huggins and Hodges, 1941); nicotine produces a secretion of shorter duration and moreover discontinues the influence through the hypogastric nerves. Atropine and ergotamine discontinue the secretion, even after stimulation with pilocarpine. Adrenalin increases the secretion, whilst acetyl choline exerts no effect (Farrell, 1938).

The pressure of the secretion after administration of pilocarpine to dogs equals from 70 to 120 cm water pressure, also according to Farrell.

Intensity of Secretion in Man.

The mature male daily excretes about 0.05 ml of prostatic secretion in the urine. This volume is fairly constant from day to day in the same individual (Scott and Huggins, 1942). The proportion of prostatic secretion in a daily ejaculation is about 1 ml, i. e. in periods without any ejaculation the secretion of the prostate is very scanty. It cannot be considered out of the question that during prolonged intervals between the ejaculations the secretion may be greater than this estimate but, if so, the excess must be resorbed again through the epithelium of the prostate.

Composition of the Normal Prostatic Secretion in Man.

This has been examined especially by Huggins, Scott and Heinen (1942). The secretion is a milky, serous, homogeneous fluid with pH about 6.5. Its content of dry matter is 6.8 per cent., the protein constitutes the 2.5 per cent. Characteristic of the prostatic secretion is its high content of calcium 30 millimol/litre) and citrate (Scherstén, 1936); further, phosphorous lipoids and cholesterol constitute the greater part of the lipoids, whilst neutral fat is present only in small quantities and lecithin cannot be detected. The lipoids are moreover present in the epithelial cells of the acini of the prostate and, according to Huggins (1945), are produced by secretion.

The acid phosphatase, which is produced in exorbitant amounts in the human prostate, will be mentioned separately in the following.

Chapter V

BIOCHEMICAL PROPERTIES OF PROSTATE PHOSPHATASE

Division of the Phosphatases.

The phosphatases are defined as enzymes which specifically promote the hydrolytic splitting of the radical R from

$$R-O-P\begin{matrix}=O\\-OH\\=O\end{matrix} \quad \text{or} \quad \begin{matrix}R-O\\ \\R-O\end{matrix}\!\!\diagdown\!\!\diagup\!\!\begin{matrix}OH\\P\\O\end{matrix}$$

R may be aliphatic (alcohols), cyclic (phenols), or the phosphoric acid rest (the substrate then being pyrophosphate).

As the phosphatases have quite a marked affinity to the phosphoric component, there is a marked specificity for the nature of the component (degree of esterification and structure). The phosphatases can therefore be classified into monophosphatases, diphosphatases, pyrophosphatases, metaphosphatases and phospho-amidases. With regard to the radical, the effect of the phosphatases is much less specific.

The monophosphatases represent the group that is most comprehensive and has been best examined. They may be divided into types according to the hydrogen ion concentration at which they have their optimum activity. Altogether the monophosphatases occurring in nature cover the entire pH range that is physiologically possible.

Classification and Chemical Properties of Prostate Phosphatase.

Prostate phosphatase is a monophosphatase belonging, according to Folley and Key's nomenclature (1936), to group A_2.

According to Kutscher and Pany (1938), it is a protein with the ion motion curve of an amphoteric electrolyte, with

its iso-electric point at pH 4.4 and with a nitrogen content varying from 12 to 15 per cent. according to the purity of the preparation. With ammonium sulphate it shows the same precipitation as globulin, and it is strikingly resistant to proteolytic enzymes. It has not been possible to demonstrate a dissociable active group (Kutscher and Pany, 1938, Kutscher and Wörner 1936 *a*, *b*). Dialysis thus does not impair the activity, on the contrary, in dialysed urine it is somewhat increased because inhibiting inorganic phosphate passes into the dialysing liquid (Kutscher, 1935, Kutscher and Pany, 1938). The dialysing liquid possesses no phosphatase effect.

Dependence of the Activity on pH.

The activity has a fairly wide optimum range about pH 5, somewhat varying with the conditions under which it is determined. The shorter the time of hydrolysis, the more accurate the determination of the pH-activity curve. With a protracted time the curve is distorted by the inactivation at the pH in question, in particular at a strongly acid or basic reaction. As there is a considerable divergence between the statements of the optimum pH by the various authors, Lundquist (1947 *b*) took up the question for renewed examination, in which the ionic strength was kept constant in spite of changing pH. He used acetate buffer and found an optimum about pH 6.3 in the splitting of the natural substrate: phosphoryl choline, and about 6.0 when the substrate was glycerophosphate or phenylphosphate.

Dependence of the Stability on pH.

The stability has its maximum between pH 4 and 6, and decreases outside this range, most abruptly on the acid side (Kutscher and Wörner, 1936 *b*). The inactivation is irreversible.

Keeping Qualities.

The keeping qualities of prostate phosphatase are very good in its physiological surroundings, the seminal fluid. Liquid semen kept in stoppered containers retains the strength almost unchanged for the first month, irrespective of putrefaction.

Inhibiting Substances.

Prostate phosphatase is competitively inhibited by fluoride, especially with regard to the glycerophosphates (Knoeve-

nagel, 1940), less with regard to phenyl phosphoric acid to which the affinity of the enzyme is greater (Kutscher and Wüst, 1941—42). Other anions, too, such as maleïnate and oxalate, may inhibit the enzyme. The inhibition with fluoride (and maleïnate) can be counteracted by citrate (Lundquist, 1947 *b*), which does not influence the oxalate inhibition.

The Mg-ion is said not to influence prostate phosphatase (Kutscher and Wörner, 1936 *b*), though Ohlmeyer (1942) maintained that the fluoride inhibition was increased by the admixture of Mg-ion.

Prostate phosphatase resembles the other acid phosphatases because of the fluoride inhibition and the lacking Mg-activation, but according to Kutscher and Wörner, (1936 *b*) it differs from them in being irreversibly inactivated by alcohol, acetone and ether; according to these authors, this is presumably due to the high degree of purity which can be attained in preparations of prostate phosphatase. However, the observation made by Herbert (1944) that by means of alcohol the prostate phosphatase can be separated from the other acid phosphatases in human serum, speaks in favour of a specific property of prostate phosphatase. The faculty of alcohol for inactivation was confirmed by Gutman and Gutman (1938 *a*) concerning the phosphatase in serum of patients suffering from metastases from carcinoma of the prostate. In tissue sections Gomori (1941) was, however, unable to find any corroboration of the inactivation with acetone, which perhaps may have been due to the presence of the other substances of the cell.

It may be mentioned in this connection that Appleyard (1948) ascertained the presence of a transphosphorylase in prostatic extract which, for instance, is capable of replacing phenolphthalein with alcohol in phenolphthalein phosphate.

According to Abul-Fadl and King (1947), prostate phosphatase differs from the erythrocyte phosphatase in not being inhibited by formaldehyde.

Chapter VI

CONTENT OF ACID PHOSPHATASE IN THE URINE

Acid Phosphatase in the Urine of Men and Women.

Scott and Huggins (1942) found the same excretion of phosphatase in the urine of either sex at ages before the thirteenth and after the seventieth year. Between these ages they found a 24-hour excretion in men which was four times the one ascertained in women. Burgen (1947) examined ten-year-groups and fixed the limits at 10 and 60 years. According to Burgen, the urine of men from the tenth to nineteenth years contains a somewhat larger quantity of phosphatase than the urine of women, and from the the twentieth to fifty-ninth years the amount of phosphatase in 24-hour urine is five times larger in men than in women. Burgen found a great variation in the 24-hour excretion from one man to another in the same age-group. According to Scott and Huggins, who followed the excretion from the same individual for several days, the excretion is, however, quite constant in the same person. In examinations of fractions of the 24-hour urine there can be demonstrated irregular, very transient rises of the excretion of phosphatase, in particular in morning urine (Dmochowski and Assenhajm, 1935, Kutscher and Wolbergs, 1935 *a*) it may be as much as ten times the average concentration of phosphatase.

Sexual Stimulation and the Passing of Prostatic Secretion into the Urine.

Scott and Huggins found an increased concentration of phosphatase only in the first portion of urine after ejaculation

but not in the subsequent portions, and therefore supposed that reflux to the bladder does not take place during ejaculation.

Writer's experiments:— The concentration of phosphatase in the first drop of urine of a preejaculatory micturition was examined in two normal, mature men. The concentration of phosphatase was 0.4 and 2.5 P. U. per ml. (1 P. U. is 1 Gutman and Gutman unit; see also page 53). As will be mentioned later, the concentration in pure prostatic secretion from normal individuals is at least 5,000 P. U. Thus the prostate does not seem to give off any secretion to the urethra in the course of erection, as is the case with Cowper's glands.

According to Scott and Huggins, the amount of prostate phosphatase passed with the urine of 24 hours averages 613 (male urine) less 163 (female urine) = 450 P. U., which — with an average concentration of phosphatase in prostatic secretion of about 10 K. P. U. (1 K. P. U equals 1000 Gutman and Gutman units; see page 53) — will correspond to about 0.05 ml, i. e. as little as one normal drop!

In the urine of a 30-year-old castrate (castrated at the age of 19) Scott and Huggins found from 100 to 150 P. U. in 24 hours. After treatment with testosterone for 3 weeks the concentration of phosphatase had risen from 5 to 15 P. U./100 ml. The authors suggest that the content of acid phosphatase in 24-hour urine be used as a measure of the production of androgens.

It may be mentioned in conclusion that the results of phosphatase analyses in urine the dilution of which is not stated should be taken with reservation, as it has been shown by Robinson and Warren (1948) that because of the presence of inhibiting substances the urine should be diluted from 5 to 20 times before the phosphatase analysis.

Chapter VII.

THE EJACULATE IN MAN

Successive Composition of the Ejaculate.

In 1911 Broesike showed that the secretions of the various genital glands are successively ejaculated. He made a microscopical examination of 3 samples of ejaculated semen secured in fractions.

The chronological sequence was as follows: —

1. One or two pre-ejaculatory drops originating from Cowper's glands which also in woman give off secretion before the orgasm.
2. Prostatic secretion containing no spermatozoa.
3. Secretion of the testis-epididymis-vas deferens containing the majority of the spermatozoa.
4. The vesicular secretion.

The purpose of the pre-ejaculatory drops is supposed to be both to neutralize the remains of urine in the urethra and to smooth the walls of its mucous membrane. The prostatic secretion of an almost neutral reaction neutralizes the urine and the acid vaginal secretion; its importance to the spermatozoa has been elucidated only in part.

The portion contributed by the testis-epididymis-vas deferens is of a very small volume (about 0.1 ml). Its consistency is rather firm, and the spermatozoa it contains do not become free and motile until the secretion is liquefied by enzymes contained in the other fraction of the seminal fluid.

At the moment of ejaculation the secretion of the vesicular glands is very viscous, and plugs the vagina in certain animals; this prevents the efflux of the portion first ejaculated.

By means of a determination of the concentration of phosphatase in the various fractions of the semen we can find an expression of the relative share of the prostatic secretion in these fractions. In 1941 Broesike's observation was confirmed in this manner by Gutman and Gutman. Later (1946) the writer observed a similar preponderance of the prostatic secretion in the first fraction of ejaculates of 3 normal men; further, that also at the end of the ejaculation prostatic secretion is ejaculated, as the last fraction contains an amount of phosphatase which is larger than the one which may originate from "contamination" of the urethral walls by the first fraction.

Broesike's view of the ejaculation as a strictly fractionated product must, therefore, be modified to the effect that the prostatic secretion is ejaculated chiefly at the beginning of the orgasm. As far as the vesicular secretion is concerned, it has appeared that the greater part of it is ejaculated last, but that some of it may also be contained in the first fraction: this was demonstrated by Lundquist (1947 *b*) who used the presence of fructose as an indicator for the vesicular secretion.

The Concentration of Phosphatase in Ejaculates of Normal Individuals and of Infertile and Subfertile Individuals.

Tables I and II show the results of the analyses of ejaculates made by previous authors and by the writer.

There is a fairly good correspondence between the mean figures indicating the concentration of phosphatase in normal ejaculates as stated by Riisfeldt, by the writer, and by Andersson and Sury (Engberg *et al.*, 1947), whereas Gutman and Gutman found a lower and Lomholt *et al.* (1946) an essentially higher mean figure, and apparently these differences cannot be explained by the methodics of analysis used. This difference is also found even when the two last-mentioned materials of analyses are made comparable to those of the other authors by including only the first ejaculate of each subject. In materials of normal individuals no author has found a minimum value of the phosphatase concentration below 400 or over 800 P. U.

The variability of the concentration of phosphatase in ejaculates of the same individual has been examined by Gutman and Gutman (1941) who found fairly constant values. The

Table I.

The Phosphatase Concentration in Ejaculates of Normal Persons and Patients determined by Previous Authors and the Writer.

Authors	Number of ejaculates	Number of individuals	Nature of series	Minimum phosphatase concentration in P.U.	Maximum phosphatase concentration in P.U.	Mean value in P.U.
Gutman *et al.*[1])	43/10		normal	540	4220	
(—	14/14		normal	810	4220	1950)
—	24/24		sterility	33	the rest within normal limits	
Lomholt *et al.*[2])	47/26		normal	800	13200	5500
(—	26/26		normal	800	13200	ca. 5500)
Riisfeldt [3])	149/149		normal + sterility	400	8000	2660
Andersson [4])	173/173		normal	ca. 500	ca. 8900	3767
—	54/54		aspermia	ca. 500	ca. 5900	3434
Engberg *et al.*[4])	16/16		cryptorchismus	750	3900	2061
Sury [4])	50/50		normal			4400
—			aspermia			3300
From Hansen [5])	32/32		normal	400	9800	3900
—	25/25		infertilitas m. g.	800	11800	3320
—	26/26		aspermia	1000	8100	3440
From Hansen [6])	30/30		normal + sterility	500	7700	3000

[1]): Gutman and Gutman 1941.
[2]): Lomholt, Rasmussen and Schønheyder 1946.
[3]): Riisfeldt 1946.
[4]): Engberg, Andersson, Sury and Raft 1947.
[5]): From Hansen 1946.
[6]): From Hansen, present work, see Table II.

greatest variation was from 1,630 to 2,915 P. U. in 6 succesive ejaculates and the lowest was from 3,160 to 3,350 in 5 samples. So good a reproduction could not be obtained by Lomholt *et al.*. In more than half the number of cases they found considerable variations but stressed that individuals who show a remarkably low concentration of phosphatase in the ejaculate will always do so in repeated examinations.

Neither Riisfeldt (1946) nor Delory (1947) found any correlation between the concentration of phosphatase on the one hand and pH in the semen, the volume of the semen, the number, the concentration and the motility of spermatozoa or the number of abnormal forms of spermatozoa on the other hand.

Table II.

WRITER'S EXAMINATIONS

The Phosphatase Concentration in 30 Ejaculates from 30 Men, partly Normal, partly Infertile.

Phosphatase Concentration in K.P.U.	log Phosphatase Concentration
0.5	— 0.30
0.9	— 0.05
1.5	0.18
1.6	0.20
1.7	0.23
1.8	0.26
1.8	0.26
2.3	0.36
2.4	0.38
2.7	0.43
2.8	0.45
2.8	0.45
2.8	0.45
3.2	0.51
3.4	0.53
3.5	0.54
3.5	0.54
3.5	0.54
3.6	0.56
3.7	0.57
3.8	0.58
3.8	0.58
4.7	0.67
4.7	0.67
4.8	0.68
4.8	0.68
6.7	0.83
7.6	0.88
7.7	0.89
7.7	0.89

If log phosphatase concentration is supposed to be of normal distribution, we have: mean figure $\pm$ 2 $\times$ standard deviation = 0.48 $\pm$ 2 $\times$ 0.27 corresponding to *a mean phosphatase concentration of 3.0 K. P. U.* with the 5 % limit at 0.9 to 10.2 K. P. U.

Proportion of Prostatic Secretion in the Ejaculate.

The proportions contributed by the various sexual glands vary much in different animals. In the boar, for instance, the prostate and the urethral glands supply one half of the ejaculate, the vesicular glands one-fourth, Cowper's glands (which are very large in this animal) supply one-fifth, and the testis-epididymis-vas deferens a few per cent. (McKenzie *et al.*, 1938). In man the proportion of prostatic secretion can be calculated from the following formula:

Volume of prostatic secretion × phosphatase concentration in prostatic secretion =
volume of ejaculate × phosphatase concentration in ejaculate.

In a material consisting of expressed prostatic secretion from 25 normal males at ages from 17 to 55 years an average phosphatase concentration of 14,500 P. U. was found, and in 32 ejaculates from as many fertile males an average phosphatase concentration of 3,900 P. U. was ascertained by the writer (1946). According to these figures, the proportion of prostatic secretion in the ejaculate averages 27 per cent. In the present material of prostatic secretion from 33 normal males from the twentieth to the fifty-ninth year (mean figure: 10.5 K. P. U.) and 30 ejaculates (mean figure: 3.0 K. P. U.) the mean proportion was 29 per cent. In a similar manner Lomholt *et al.* found the proportion $5{,}500 \times 100 \div 21{,}000 = 26$ per cent. By far the greater part of the rest of the ejaculate consists of vesicular secretion.

In a single fractionated ejaculate the proportions contributed by the various glands can be calculated as shown by Lundquist (1947 *c*) who used, respectively, acid phosphatase, fructose, and spermatozoa as indicators for the secretions of the prostate, the vesicular glands and the testis-epididymis-vas deferens. In 5 complete ejaculates he found that the proportion of the prostatic secretion was about 25 per cent. (Personal communication, 1948).

Content of Prostatic Secretion in Semen after Repeated Ejaculations.

Previous examinations: Scherstén (1936) examined the content of citrid acid — as a criterion of prostatic secretion — in semen ejaculated twice at an interval of a few hours and found a fall of the concentration, as the last ejaculate in 4 of these experiments in the same individual contained 44, 69, 65 and 55 per cent. of the citric acid concentration of the first ejaculate.

Gutman and Gutman (1941) examined the influence of frequent ejaculations on the content of phosphatase in semen. In two samples ejaculated at an interval of one hour they found that 3 normal males displayed a variation of the phosphatase concentration from 1,130 to 880, from 2,550 to 2,180 and from

1,600 to 2,600 P. U., and in two samples of semen ejaculated at an interval of 8 hours: 1,620 and 1,890. They conclude that the difference between the concentration of phosphatase in the first and the second ejaculations is of the same magnitude as the one found in samples of semen ejaculated at one week's interval. It may be stated for comparison that the protein content in seminal fluid is reduced by frequent ejaculations but is re-established after an interval between the ejaculations of from 1 to 3 days (Huggins, Scott and Heinen, 1943).

Writer's Examinations:—

For the purpose of examining the relation between the available amount of secretion in the prostate and the quantity ejaculated during an orgasm, two persons were examined; Table III gives the results of determinations in repeated, rapidly successive ejaculates. Both subjects suffered from a mild chronic prostatitis with only few symptoms. Experiment No. 1 (subject A)

Table III.

Influence of Ejaculations in Rapid Succession on the Phosphatase Content of the Ejaculate.

Subject	Experiment No.	Ejaculate No.	Hour of ejaculation	Phosphatase concentration in ejaculate in P.U.	Volume of ejaculate in ml	Amount of phosphatase per ejaculate	Amount of phosphatase in per cent of content in 1st ejaculate	Number of spermatozoa in millions per ml
A	1	1	0	790	3.5	2770	100	
		2	1^{15}	522	1.5	780	28	
		3	3^{15}	322	0.6	193	7	
A	2	12. ej. in 4 days		185				
B	3	1	0	3140	3.2	10040	100	24.0
		2	0^{05}	3650	1.8	6570	65	4.25
		3	0^{10}	2200	1.4	3080	30	3.25
		4	2^{40}	3340	2.3	7680	76	0.45

shows a fairly effective evacuation of the available prostate phosphatase, as three-fourths are evacuated with the first of 3 ejaculates. In subject B it proved considerably more difficult to evacuate the available amount of phosphatase, as ejaculations 2 and 3 together contained as much phosphatase as the first ejaculate; any formation of fresh phosphatase is out of the question in this experiment because of the short intervals between the ejaculations. The increased ejaculation of phosphatase 2½ hours later may be due both to a production of phosphatase during the interval and to an increase of the ejaculatory force. The ejaculation of spermatozoa shows

no such remission, which is in conformity with Lode's finding that spermatozoa were present in the first and second but not in the third portion of seminal fluid ejaculated during the same nigth.

Influence of Sex Hormones on the Ejaculate.

According to Heckel and Steinmetz (1941 *a*), the administration of testosterone propionate even in full doses does not influence the volume of the ejaculation. These authors examined 12 patients suffering from hypertrophy of the prostate. They concluded that neither the proportion supplied by the prostate nor the one supplied by the vesicular glands to the ejaculate is changed under the influence of androgens.

But the proportion derived from the vesicular glands, and thus the total volume of the ejaculation, is reduced under the administration of oestradiol benzoate. Heckel and Steinmetz (1941 *b*) thus found that the decrease began after a period varying from 23 to 145 days in the course of treatment with doses from 6,000 to 12,000 R. U. of oestradiol benzoate 3 to 6 times weekly. In 4 out of 5 patients at ages from 58 to 72 years the volume was reduced to about 0.5 ml, which is from one-seventh to one half of the original volume. After the treatment had been discontinued the volume increased again. The authors did not examine the content of phosphatase and fructose and do not mention whether the decrease occurs chiefly in the secretion of the vesicular glands or in that of the prostate; as the proportion supplied by the latter to the ejaculate amounts to one-fourth (see page 42), there can be no theoretical objection to the view that by far the greatest decrease is caused by the cessation of the production of the vesicular glands.

Correspondingly Huggins and McDonald (1945) ascertained a considerable decrease of the fructose concentration and the volume of the ejaculate in 6 adult males suffering from haemospermia who were treated with 0.05 mg of ethinyl oestradiol from twice daily to 3 times weekly for periods varying from 21 days to 6 months. On the other hand, the effect on the concentration of phosphatase in the ejaculate was not unambiguous; both increased and decreased values were found. These authors consider that because the prostate is less sensitive to oestrogen, this substance has exerted a selective effect on the

vesicular glands; but if the entire quantity ejaculated were to consist of prostatic secretion that had remained uninfluenced, then the concentration of phosphatase in the ejaculate would have increased up to 4 times.

In 1947 Engberg *et al.* examined the concentration of phosphatase in ejaculates obtained from 3 cryptorchid patients once before and once after treatment with Klianyl (synthetic oestrogen), 8 mg daily for 10 days, and found increased as well as decreased values. The treatment was presumably too brief, judged by Heckel and Steinmetz's series of cases, in which the latent period varied from 23 to 119 and 145 days.

Phosphatase Concentration of Ejaculate and Prostatic Secretion in Prostatitis.

In 1946 the writer examined 3 fractionated ejaculates obtained from 3 normal males and 3 obtained from 2 patients suffering from chronic prostatitis. In accordance with the observation made by Gutman and Gutman (1941), the 3 normal subjects evacuated the prostatic secretion at the beginning of the ejaculation, whereas the 3 ejaculates of patients showed a completely suspended fractionation of the ejaculation of the prostatic secretion, i. e. it was evenly distributed in the entire ejaculation. The fractionation of the ejaculation of spermatozoa was examined in one ejaculate and was normal. In other respects, too, the physiological processes of the prostate are influenced; Lomholt *et al.* (1946) thus found a lower phosphatase concentration than the normal in ejaculates of patients who had previously suffered from gonorrhoea. As shown by Lomholt *et al.* and From Hansen and T. Jensen (1946), this is explained by the fact that the concentration of phosphatase in prostatic secretion expressed from males suffering from chronic prostatitis is considerably reduced and, as shown by repeated expression, remains at low, fairly constant values, even for prolonged periods.

In acute prostatitis the production of phosphatase in the prostate is often (always?) completely or nearly extinct (From Hansen and T. Jensen).

Writer's experiment: —

1st fraction: 1.4 P. U. × 2.0 ml = 2.8 P. U./fraction.
Spermatozoa: 0.07 mill./ml

2nd fraction: 2.8 P. U. × 5.5 ml = 12.4 P. U./fraction.
Spermatozoa: 0.03 mill./ml

3rd fraction: 0.7 P. U. × 8.0 ml = 5.6 P. U./fraction.
Spermatozoa: 1.8 mill./ml

Ejaculate: 1.3 P. U. × 15.5 ml = 20.8 P. U./ejaculate.

As shown by the experiment above, it may be impossible to ascertain the presence of phosphatase even in the first fraction in case of acute prostatitis. The patient suffered from an acute (post-)gonorrhoeal prostatitis with a considerably enlarged, tender gland.

Macroscopically the semen was distinctly changed, it was brownish, thin and transparent in all fractions, and very copious; so great a volume of seminal fluid has not been described previously. The production of phosphatase of this patient had been discontinued. As might be expected, the fractionating of the ejaculation of spermatozoa was normal.

Proportion of Vesicular Secretion in the Ejaculate.

In examinations of 150 ejaculates obtained from 123 fertile and infertile males H a r v e y (1948) found that the concentration of fructose rises with increasing volume of the ejaculate. This positive correlation, however, applies only to quantities under 5 ml or so. Above this limit the concentration of fructose falls as the volume of the ejaculate increases. The author concluded from these findings that it is chiefly the proportion of the vesicular secretion which constitutes the volume of the ejaculate up to 5 ml, whereas increases in volume over 5 ml are chiefly due to increased ejaculations from the other genital glands.

The author moreover found that most of the available vesicular secretion is evacuated during a single ejaculation, and that the same concentration of fructose in the ejaculate is not found until there has been an interval of 48 hours between the ejaculations.

Chapter VIII

PREVIOUS EXAMINATIONS OF THE CONNECTION BETWEEN HYPANDROGENIC CONDITIONS AND THE PRESENCE OF VARYING SUBSTANCES (EXCLUDING PHOSPHATASE) IN THE EJACULATE

In 1942 H u g g i n s *et al.* stated that the concentration of proteins in the ejaculate is low in individuals who have a defiency of androgens, but that it rises after treatment with testosterone propionate.

In 1947 M a n n and P a r s o n s showed that the fructose in the secretion of the vesicular glands of the boar is an accessory sex character, as the content in the ejaculate subsides after castration, whilst both the concentration and the absolute amount of fructose rises to normal values after implantation of testosterone propionate; also, the effect of castration on the formation of fructose can be obviated by early treatment with testosterone propionate. In the course of the pubescence of the rabbit, fructose appears in the organ homologous with the vesicular glands some time before the spermatozoa become motile (D a v i e s and M a n n, 1947).

Lastly, H u m p h r e y and M a n n (1948) have shown that the concentration of citric acid in ejaculates of rabbits is reduced by castration and rises under treatment with testosterone.

Chapter IX.

PREVIOUS EXAMINATIONS OF THE PRODUCTION OF PHOSPHATASE IN HYPANDROGENIC CONDITIONS

Introduction.

As will appear from the preceding pages, quite a voluminous literature on acid prostate phosphatase has gradually been produced. The examinations that have been made have been directed chiefly towards the occurrence of the enzyme in prostatic secretion, ejaculate and urine of normal individuals and of patients suffering from prostatitis or infertility; and a partial recognition of the biochemical function of the enzyme in the seminal fluid — the decomposition of phosphoryl choline — has also been attained.

On the other hand, only few examinations of the connection between the sex hormones and prostate phosphatase have been published so far. As already mentioned, Gutman and Gutman (1939) showed that androgens but not oestrogens are capable of starting a production of phosphatase in prepubertal monkeys. Clinical examinations of such a connection have, however, been published only in the following few works:

In 1942 Scott and Huggins examined the urine of a 30-year-old castrate and found a diminished quantity of phosphatase, which increased under the administration of testosterone propionate. The authors suggested that the content of phosphatase in 24-hour urine be used as a measure of the production of androgens in the organism.

In a publication of 1944 Watkinson *et al.* pointed out that they found enormous quantities of phosphatase in the

semen of normal males but only little in a sample of semen of a eunuchoid.

In a series of cases comprising 22 patients who showed signs of defective sexual maturity the writer, in 1945, showed that a diminished concentration of phosphatase was frequently found in prostatic secretion obtained by digital massage, that the size of the concentration was correlated with the degree of hypandroid development — judged by the somatic sex characters present — and, further, that the concentration increased under treatment with chorionic gonadotropin.

Lastly, in a series of patients comprising 16 cryptorchids, Engberg *et al.*, in 1947, demonstrated a lower concentration of phosphatase in the ejaculate and a lower renal androgen excretion than the normal, and found a positive correlation between these two qualities.

Chapter X

WRITER's EXAMINATIONS OF THE CONCENTRATION OF PHOSPHATASE IN EXPRESSED PROSTATIC SECRETION

Introduction.

The four communications mentioned in the preceding chapter, show that the production of phosphatase by the prostate in man is influenced by the production of androgens in the organism, but it seems necessary to examine to how great an extent the output of testis hormone is responsible for this production of phosphatase, and what is the importance of other hormones in the organism in this respect. Provided that the production of phosphatase then proves to be a suitable indicator of the production of testis hormone it will afford information not only about the spontaneous function of the Leydig cells in normal and diseased conditions but also about the influence of gonadotropins or the endocrine apparatus of the testes. Lastly, by following the phosphatase reaction it will be possible to obtain a certain knowledge of the course of the spontaneous puberty.

The points briefly outlined above are the main subjects of the examinations which will be accounted in the following.

TECHNIQUE OF THE METHODS OF EXAMINATION USED IN THE PRESENT WORK

The methods of examination may be divided into two main groups:

(1) Determination of the concentration of phophatase in expressed prostatic secretion and in ejaculate, and determi-

nation of admixtures to the prostatic secretion during expression.

(2) Measurement of certain sex characters.

re 1. — Determination of the concentration of acid phosphatase in expressed prostatic secretion and in ejaculate.

— Quantitative determination of admixture of urine, if any, to the expressed prostatic secretion.

— Quantitative determination of admixture of vesicular secretion, if any, to the expressed prostatic secretion.

re 2. — Measurement of the volume of the testes.

— Measurement of the dimensions of the penis.

— Estimation of the degree of the growth of pubes and other accessory hair.

— Estimation of the size of the prostate.

— Estimation of the appearance of the expressed secretion.

— Quantitative determination of the content of gonadotropic, androgenic and oestrogenic substances in the 24-hour urine.

— Ascertaining the degree of ossification.

Determination of the concentration of acid phosphatase in expressed prostatic secretion.

The prostatic secretion is obtained by digital massage of the prostate in the longitudinal direction, first of the lobes, and last in the midline after urine which may possibly be present in the urethra has first been removed by "milking" and the urethral orifice has been wiped. The secretion is drawn into a capillary tube as it is expressed, and air vesicles are interposed. The ends of the tubes are closed with vaseline, and the tubes are then kept in an ice-box till the analysis is made; but phosphatase is not impaired even when kept at room temperature for days. Before the analysis the ends containing vaseline are sawn off.

The analysis is a modification of G u t m a n and G u t m a n's methods (1938 *a*) and is made as follows:

T e s t s y s t e m.

The expressed prostatic secretion is dealt with in one of the three ways mentioned on page 54, the principle is, that 10 mm^3 of the secretion is run out of a so-called Carlsberg semi-automatic micropipette. The suitable dilution was made with

1, 2, 5, 10, 20, 25 or 50 ml physiological saline solution according to the supposed concentration of phosphatase which is judged from the appearance, which may vary from aqueous to milky. After shaking, a quantity of 100 mm^3 from each of the two dilutions is added by means of a Carlsberg pipette to 10 ml of a buffer substrate solution that has been heated in advance at 37° C. and contains 10.9 mg of disodium monophenyl phosphate in a citrid acid-citrate buffer solution composed of 21 cg of citric acid (pure) and 7.5 cg of sodium hydroxide (pure). (As the content of water in sodium hydroxide varies, the solution should be adjusted electrometrically at pH 4.8. The change of molarity taking place in this manner is of no consequence to the hydrolysis. If the buffer solution has not been prepared immediately before use, it should be boiled before the admixture of phenyl phosphate, as fungi which may contain disturbing quantities of phosphatase are then killed, and their enzyme is inactivated). The contents are mixed and the test-tube is allowed to stand for 15 minutes at 37° C., after which 1 ml of Folin and Ciocalteu's phenol reagent (prepared according to H. B u c h's method, 1942) is added; this is mixed, and an admixture is made of 4 ml nearly saturated sodium carbonate solution, purified by means of activated carbon.

(Because of the difficulties in procuring soda with a known content of water, the "nearly saturated" sodium carbonate solution was chosen in preference to the 20 per cent. solution generally stated. The solution should be so concentrated as to produce clear blue colours without any greenish tinge. When this is the case the coefficients of inclination of the various standard curves only differ slightly from each other).

The contents are mixed again and the test tube is left for about 15 minutes at 37° C. until the blue colour has been fully developed; the coefficient of extinction is then read photometrically in a "Leifo" photometer. After deduction of the coefficient of extinction of a blank test the corresponding phenol concentration is read from a standard curve, after which the concentration of phosphatase in the expressed prostatic secretion is calculated with due regard to the dilution made.

When the volume of the expressed secretion was less than 20 mm^3, a quantity of only 10 mm^3 were added, after suitable dilution, to each of the two hydrolysis systems.

The b l a n k s y s t e m is prepared in the same manner as the test system, only the admixture of the diluted secretion is omitted. Theoretically 100 mm^3 of the diluted secretion should be added to the blank system after the admixture of the phenol reagent but, as it does not change the coefficient of extinction of the blank system to any measurable degree (the amount of secretion added would be 1 mm^3 at the utmost; the increase in volume of the system would only be 1 : 150), it has been omitted, and the same blank system was then used for all the test systems made on the same day.

S t a n d a r d s y s t e m s are blank systems to which a known quantity of standard phenol solution has been added before the admixture of the phenol reagent. Whenever a fresh portion of phenol reagent or carbonate solution was taken into use, 2 standard systems were made, containing, respectively, 50 and 100 mm^3 of the same arbitrarily chosen standard phenol solution, which by means of iodometric titration a d m o d u m H o l d e (1924) was found to contain 0.2173 per cent. of phenol. Whenever tested, these two standard systems only differ slightly, or do not differ at all, from the blue colour which may be expected according to a standard curve made once and for all from many standard systems.

The **phosphatase unit** has been fixed at **1000 times the quantity of the enzyme per ml of secretion which in one hour splits off 1 mg of phenol from the said system.** This unit of phosphatase concentration is termed K. P. U. (= kilophosphatase unit, implying per ml); 1 K. P. U. = 1000 Gutman and Gutman units (per ml)).

The following is an example of the calculation of the concentration of phosphatase: A quantity of 10 mm^3 of secretion is added to each of two test-tubes for dilution with 5 ml of physiological saline solution; 100 mm^3 of this mixture (i. e. 0.2 mm^3 of secretion) are added to each of two hydrolysis systems the extinction coefficients of which, after hydrolysis for 15 minutes, are found to be 0.661 and 0.646. The extinction coefficient of the blank system, measured to be 0.053, is deducted from these two values, the result being 0.608 and 0.593. From the standard curve the quantities of phenol split off in the course of the period of hydrolysis (15 minutes) are found to be 0.0972 and 0.948 mg. Converted to 1 ml of secretion and

hydrolysis for an hour the quantity of phenol split off is: $0.0972 \times 5000 \times 4 = 1.944$, respectively $0.0948 \times 5000 \times 4 = 1.896$. The mean figure is then 1.920 gm of phenol. The concentration of phosphatase is then 1.9 K. P. U. (per ml).

Determination of the Concentration of Phosphatase in Ejaculate.

The analysis is made in the same manner as is stated for expressed secretion; after careful mixing, a quantity of 10 mm^3 is run out of a pipette into each of 2 test-tubes for mixing. The optimum dilution is generally attained by the admixture of from 2 to 5 ml of physiological saline solution.

Accuracy of the Phosphatase Analysis.

As all variations observed in the production of phosphatase depend on determinations of the concentration of the enzyme in expressed prostatic secretion, a few, however, on determinations of its concentration in ejaculates, it is important to be able to form an estimate of the reliability of the method of measuring, i. e. an estimate of the error of the determination. A large material of duplicate determinations has therefore been analysed.

This material is divided into three groups of duplicate determinations; after drawing the expressed secretion into capillary tubes, one of three different procedures was used for the duplicate determinations:

Group 1 comprises 245 duplicate determinations made in the following manner:

(a) A quantity of 10 mm^3 is drawn from either end of the capillary tube by means of a pipette.

(b) Each of these volumes is diluted with a suitable quantity of saline solution, the same quantity for each volume, and 100 mm^3 of each dilution are added to the buffer-substrate system for hydrolysis for 15 minutes at 37° C.

Group 2 comprises 159 duplicate determinations made as follows:

The contents of the entire capillary tube were first homogenized in a small test-tube by means of a current of air, after which 2×10 mm^3 of the mixture were run out of a

pipette. Each of these volumes was then dealt with as described in 1 (b).

In both these groups duplicate samples of the secretion were thus taken. If a greater error of determination is found in Group 1 than in Group 2, it must mean that there has been a different concentration of phosphatase in the two ends of the capillary tube, i. e. the concentration of the enzyme varies in the same quantity of expressed secretion.

Group 3 comprises 131 duplicate determinations made as follows:

A quantity of 10 mm^3 is drawn by means of a pipette from the end of the capillary tube containing the amount first expressed. A suitable quantity of saline solution is added. Then 2×100 mm^3 of this dilution are run out of a pipette into the buffer-substrate-system for hydrolysis for 15 minutes at 37° C.

Group 3 thus consists in duplicate tests with the dilution. If Group 2 shows a greater error of determination than Group 3, the difference must be due to the uncertainty in running out of the pipette 10 mm^3 of the expressed secretion.

To examine whether the error of determination depends on the size of the concentration of phosphatase, a further division was made in each of the three groups according to the magnitude of the mean figure of each duplicate determination, a distinction having been made between 4 different levels of the concentration of phosphatase: —

	<	1 K. P. U.
1 to	<	5 „ „ „
5 to	<	10 „ „ „
	≧	10 „ „ „

It appeared at once that there was a very great error in the determination of concentrations < 1, which had also been expected. As at least 1 ml was used to dilute the expressed secretion, such secretions as have a very low concentration of phosphatase will produce vrey pale colours in the test system. The error in reading the photometer thus becomes greater, and the extinction of the blank system will also, respectively, constitute so large a subtrahend that the error of determination must be great.

For this reason the values < 1, i. e. all expressed secretions

in which the mean figure of the duplicate determination is under 1 K. P. U., have not been considered in the calculation of the error of determination.

It should be endeavoured in the colorimetric determinations to work within the range of the scale which represents the colour intensity that is most easily read. This is achieved by diluting the expressed secretion to a suitable degree and by adjusting the column of liquid in the colorimeter at a proper height. As the figure representing the concentration of phosphatase is then arrived at by multiplication by these quantities, the error of determination might be expected to be approximately proportioned to the size of the concentration of phosphatase. This may also be expressed as follows: the error in determining the logarithm of the concentration of phophatase may be expected to be fairly constant, independent of the level of the concentration of phosphatase. It has therefore been attempted to calculate the error in determining the logarithm of the concentration of phosphatase.

Table IV shows an example of the calculation of the errors of determination; it gives the figures of Group 2, the values from 1 to < 5, which contains 65 duplicate determinations.

Table IV

Sixty-five Duplicate Determinations of the Concentration of Phosphatase (Pc) in expressed Prostatic Secretion (see text).

Table IV a

No.	Pca	Pcb	d(x 10^3)	d^2 (x 10^6)	chi-square	P
1	4.07	3.84	26	676	0.57	30—50
2	4.90	5.09	17	289	0.24	50—70
3	2.03	1.99	8	64	0.05	80—90
4	3.70	4.08	43	1849	1.57	20—30
5	1.38	1.38	0	0	0	95—100
6	3.62	4.18	62	3844	3.26	5—10
7	1.94	1.87	16	256	0.22	50—70
8	1.25	1.25	0	0	0	5—10
9	3.39	3.48	12	144	0.12	70—80
10	3.39	3.30	11	121	0.10	70—80
11	1.13	1.18	19	361	0.31	50—70
12	3.84	3.69	17	289	0.24	50—70
13	1.34	1.22	41	1681	1.42	20—30
14	2.70	2.76	10	100	0.09	70—80
15	1.69	1.86	42	1764	1.49	20—30
16	1.96	1.66	72	5184	4.40	2—5
17	5.01	4.95	5	25	0.02	80—90
18	2.30	2.36	11	121	0.10	70—80
19	4.77	4.89	10	100	0.09	70—80
20	4.88	4.88	0	0	0	95—100
21	3.00	3.00	0	0	0	95—100

Table IV a (cont.)

No.	Pc_a	Pc_b	$d(\times 10^3)$	$d^2(\times 10^6)$	chi-square	P
22	4.17	4.12	5	25	0.02	80—90
23	2.87	2.98	16	256	0.22	50—70
24	1.41	1.72	87	7569	6.41	1—2
25	3.55	3.61	8	64	0.05	80—90
26	2.76	2.72	6	36	0.03	80—90
27	2.84	2.88	6	36	0.03	80—90
28	2.46	2.30	29	841	0.71	30—50
29	3.82	4.08	29	841	0.71	30—50
30	2.93	3.02	13	169	0.14	70—80
31	2.14	2.27	26	676	0.57	30—50
32	1.58	1.40	53	2809	2.38	10—20
33	2.62	2.41	36	1296	1.10	20—30
34	4.49	4.95	43	1849	1.57	20—30
35	3.64	3.36	35	1225	1.04	30—50
36	3.40	3.40	0	0	0	95—100
37	4.95	4.41	51	2601	2.24	10—20
38	4.60	4.54	6	36	0.03	80—90
39	3.14	3.42	37	1369	1.16	20—30
40	3.16	3.20	5	25	0.02	80—90
41	2.33	2.30	5	25	0.02	80—90
42	3.04	3.00	6	36	0.03	80—90
43	3.63	2.24	210	(44100)		
44	2.30	2.08	44	1936	1.64	20—30
45	3.03	3.00	4	16	0.01	90—95
46	3.32	3.32	0	0	0	95—100
47	4.46	4.40	6	36	0.03	80—90
48	4.15	4.10	5	25	0.02	80—90
49	1.28	1.28	0	0	0	95—100
50	4.10	3.94	18	324	0.28	50—70
51	1.48	1.46	6	36	0.03	80—90
52	3.35	3.06	39	1521	1.29	20—30
53	4.53	4.88	32	1024	0.87	30—50
54	1.59	1.48	31	961	0.81	30—50
55	2.96	2.96	0	0	0	95—100
56	2.98	2.82	24	576	0.49	30—50
57	1.33	1.09	87	7569	6.41	1—2
58	2.93	3.15	31	961	0.81	30—50
59	1.86	1.95	20	400	0.34	50—70
60	3.75	3.84	10	100	0.08	70—80
61	2.15	2.09	12	144	0.12	70—80
62	5.02	2.21	357	(127447)		
63	3.51	3.42	11	121	0.10	70—80
64	3.42	4.72	140	19600	16.61	0.1
65	1.77	1.67	25	625	0.53	30—50
				74627		

Σd^2 (without nos. 43 and 61) = 0.074627

$f = 2 \times 63 = 126$

$s^2 = \frac{0.074627}{126} = 0.000592$

Pc_a: 1st analysis of duplicate determination. Pc in K. P. U.

Pc_b: 2nd — — — — — — —

d: log Pc_a —log Pc_b

Table IV b

"Probability limits" P	expected distribution	distribution observed (column 6)	qui-square
0—10	6.3	6	0.01
10—30	12.6	10	0.54
30—50	12.6	10	0.54
50—70	12.6	7	2.49
70—90	12.6	22	7.01
90—100	6.3	8	0.46
f = 5	63	63	11.05
P = 5.0%			

Pc_a and Pc_b are the concentrations of phosphatase found at, respectively, the first and the second determination in the duplicate tests. d is the difference between the two determinations, i. e. $d = \log Pc_a - \log Pc_b$.

The best estimate of the error of determination, s, is given by the formula

$$s = \frac{d^2}{2n}$$

where n is the number of duplicate determinations.

In order to examine whether this estimate may be the true error of determination, the values

$$\frac{^1/_2\, d^2}{s^2}$$

are found; they should then vary in accordance with the chi-square distribution. To obtain a fairly acceptable chi-square distribution in this group, it proved necessary to disregard duplicate tests 43 and 62 as gross errors. s^2 then becomes

$$\frac{0.074627}{2 \times 63} = 0\ 000592$$

and $s = 0.0243$

The chi-square values are stated in the last column but one of Table IVa. The last column shows the probability limits (P) of the chi-square values found, read from Fisher and Yate's Statistical Tables, 1938.

We may then examine the correspondence between the ascertained distribution of P and the expected distribution, the latter being an even one from 0 to 100 per cent. In Table IVb the P-values are arranged in 6 groups, and column 2 of this table shows the theoretically expected distribution of 63 P-values to these groups. Column 3 shows the P-distribution actually found.

The conformity between the expected and the ascertained P-distribution is fairly good. Column 4 shows that this conformity was examined by means of another chi-square test which gave P = 5.0 per cent. It appears, however, that there is an accumulation of high P-values corresponding to a preponderance of low chi-squares in Table IVa.

The other groups of duplicate determinations were analysed by means of the same procedure, and the total result is stated in Table V. The error of determination (s) proves to be independent of the level of the concentration at which the determination was made. It appears that the greatest error of determination was found in Group 1. It must therefore be supposed that in many cases there has been a difference between the concentrations of phosphatase in the first and last portions of the expressed secretion drawn from the two ends of the capillary tube.

Further, the error of determination in Group 3 seems to be greater than in Group 2. As the duplicate test in Group 3 consist in 2 examinations of the same dilution of expressed secretion, this can be explained only by supposing that this dilution is not always homogeneous, so that differences may occur between the content of phosphatase in two samples of

Table V

Standard Deviation of the Determination of the Concentration of Phosphatase calculated from a Total of 501 duplicate Determinations of the Concentration in Expressed Prostatic Secretion (see text).

	The value of phosphatase concentration		Number of dupl. tests included	d^2 (x 10^6)	s^2	s	Number of dupl. tests rejected
	1-<5	K. P. U.	107	580776	0.002713	0.0521	17
Group 1	5-<10	—	58	357983	0.003086	0.0556	6
	≧10	—	52	230658	0.002218	0.0471	5
			217	1169417	0.002694	0.0514	28
	1-<5	—	63	74627	0.000592	0.0243	2
Group 2	5-<10	—	49	72787	0.000743	0.0273	0
	≧10	—	45	59154	0.000657	0.0256	0
			157	206568	0.000658	0.0256	2
	1-<5	—	41	102456	0.001250	0.0354	1
Group 3	5-<10	—	39	97207	0.001246	0.0353	1
	≧10	—	47	61652	0.000656	0.0258	2
			127	261315	0.001029	0.0321	4

100 mm^3 of the same dilution. This irregularity should be less pronounced when the expressed secretion has been homogenized in advance with a current of air as in Group 2. This should be considered in estimating the fact that in each of the 9 groups there is an accumulation of low chi-square values as in the group in Table IV described in fuller detail above. It may be that a similar accumulation of low chi-square values is also present in many other statistical examinations of materials of a similar nature, but nevertheless it was attempted to find an explanation in the technique of determination. The accumulation is due to the fact that each group contains a number of analyses showing a great difference between the duplicate tests, but it was not considered justifiable to reject them as gross errors to any greater extent than has actually been done.

Table V shows that of 290 duplicate determinations in Groups 2 and 3 only 6 were rejected as gross errors. (The fact that it was necessary to reject 28 out of 245 duplicate determinations in Group 1 just affords additional proof that this group did not comprise actual duplicate tests but different portions of expressed secretion with an often varying content of phosphatase). It was attempted to find the cause of the occurrence of a number of comparatively great differences between the duplicate tests in Groups 2 and 3; it was examined whether there might be any correlation between d and admixture of urine or mucus (secretion of Cowper's glands), between d and the degree of dilution chosen, or between d and the intensities of colour read from the colorimeter; but no such correlation was found.

Table VI

Repeated Determination of the Concentration of Phosphatase (Pc) in expressed Secretions showing a great Difference between the two Determinations in the first Duplicate Test.

Group (see page 54)	Pc in K. P. U in first duplicate determination	Pc in K. P. U. in repeated duplicate determination	The repeated determinations were made by
1	3.2 10.8	9.8 9.0 9.4	same dilutions as in first analysis without further admixture
1	8.3 4.0	4.2 3.9 4.0	do do do

Table VI (cont.)

Group (see page 54)	Pc in K. P. U. in first duplicate determination	Pc in K. P. U. in repeated duplicate determination	The repeated determinations were made by		
1	4.3 6.1	5.4 5.5 5.4	do	do , but after further admixture	
1	10.1 6.4	9.4 6.0	do	do	do
1	11.0 5.4	11.0 5.4	do	do	do
1	5.0 7.1	4.7 4.1	do	do	do
1	5.5 3.2	4.1 5.2	new dilutions of 2 samples from centre of expressed secretion		
1	5.7 2.6	2.5 3.9	do	do	do
1	15.0 6.6	12.4 6.8	new samples from first and last portions of remaining expressed secretion		
1	17.3 10.2	17.3 17.3 17.3	do	do	do
1	1.2 1.7	1.5 1.5 1.5	new samples from a mixture of remaining expressed secretion		
1	1.2 4.5	4.9	new sample from remaining expressed secretion		
1	14.0 10.4	13.4	do	do	do
2	6.4 11.1	10.3 10.7 10.5	new dilutions of 2 samples from remaining mixture of expressed secretion		
2	2.3 6.4	5.6 5.6 5.6	do	do	do
2	9.0 16.0	14.3 13.0 13.7	do	do	do
2	13.0 5.1	11.9 11.6 11.1	do	do	do
2	9.9 4.1	10.3 9.7 10.0	do	do	do

An examination of a series of duplicate determinations in which known solutions of phenol were used instead of expressed secretion showed that the error of determination was minimal as compared to that of the determination of the concentration of phosphatase in expressed secretion. The cause of the greater error of determination in the analyses of expressed secretion must therefore presumably be the inhomogeneity and consistency of the secretion. In order further to elucidate this point the determination of the concentration of phosphatase was repeated with 18 duplicate samples (13 of Group 1, and 5 of Group 2), which had shown great variations in duplicate determinations. The result of this second analysis are given in Table VI. It shows that in 10 out of the 18 cases, including all Group 2 samples, the results are identical in the repeated examinations, and the results of the second analysis are in only one case in the vicinity of the lower of the two figures found in the original duplicate determination; in all the other cases near the higher of the two figures. This may be explained by the view that the possibilities of error consisting in the admixture of other genital secretions to portions of the expressed secretion will tend to reduce the concentration of phosphatase.

In 6 cases, all of Group 1, the renewed duplicate determination has as different results as the first, which shows distinctly that the difference is due to heterogeneous composition of the various portions of the expressed secretions.

The conclusion of these reflections must be that the method used in Group 2 for the duplicate determination, after thorough homogeneization of the expressed secretion with a current of air, has been the most suitable one, because it gives the best impression of the average concentration of phosphatase of the entire expressed secretion. But even when this procedure is adopted there will still be a number of duplicate determinations which differ comparatively much because of the consistency and inhomogeneity of the expressed secretion. In such cases it will be reasonable to fix the concentration of phosphatase at the higher of the two values found in the determination.

The error of determination calculated for Group 2 is $s = 0.0256$ (see Table V). The error of the mean figure of a dupli-

cate determination is $s_m = s \div \sqrt{2} = 0.0181$. Consequently, there should be less than a 5 per cent risk of the actual value of the determination being outside the range $m \pm 0.036$, in which m = the logarithm of the mean figure. Or in other words, the actual mean figure is probably somewhere between the mean figure ascertained multiplied by 1.087 and divided by 1.087, i. .e it will not differ more than 9 per cent. from the mean figure ascertained.

The calculation of this error of determination is thus encumbered with the quite gross errors which are attributed to the consistency and inhomogeneity of the expressed secretion. A more thorough statistical analysis has shown that the necessary condition of the calculation of the error of determination — namely that the difference, d, of the duplicate error, belongs to a population of normal distribution — does not exist. The consequence is the mentioned preponderance of low chi-square values, of which Table IV shows an example. The irregular distribution of d may, however, be described in the manner that the d-values occur in two different normal distributions with different standard deviation. In other words, the series may be described as consisting of 2 groups of duplicate determinations, one with a small error of determination, the other one with a gross error in addition.

However, as the error of determination proves in all cases to be small as compared to the variations of the concentration of phosphatase which we have to deal with in the present work, more detailed statistical explanations and deliberations would fall outside this scope.

On the basis of the considerations described above, the following arbitrary formula was used in the cases where a great difference was found between two results of a duplicate determination.

When the first result of determination less the second result of determination was greater than 10 per cent. of the first result and of the second, the higher one of the two values was used.

Apart from a minimal number of cases in which the procedure according to this formula had to be used, all the concentrations of phosphatase in expressed prostatic secretion and

ejaculated semen stated in the present book are mean figures of duplicate determinations.

Determination of Admixture of Urine, if any, to the Prostatic Secretion.

Urine was detected by means of creatinine which is always, though to a varying degree, present in urine. The examination is made as follows: A certain amount of expressed secretion (50 mm^3 at the utmost) is run out of a pipette into a small test-tube, and 1 ml of a saturated picric acid solution is added. The mixture is shaken and left in an ice-box for sedimentation; for practical reasons it is allowed to stand for a week. Then 0.50 ml of the supernatant liquid is sucked up by means of a pipette, and an admixture of 50 mm^3 of a 10 per cent. sodium hydroxide solution is made. This is shaken and left for a few minutes till the colour has developed completely.

In the absence of creatinine the colour becomes an almost pure yellow with an orange tinge. If creatinine is present, the liquid assumes a reddish colour. This is now compared with the colour of corresponding comparators containing picric acid, sodium hydroxide and urine — as far as possible the urine of the individual passed immediately after the expression — in suitable quantities; for example, 5 and 10 mm^3 of urine, each with an admixture of 1 ml of picric acid and 100 mm^3 of a 10 per cent. sodium hydroxide solution, will often be suitable. This test cannot afford more than rather a rough estimate of the proportion of urine present.

As there is only a small quantity of expressed secretion left in most cases when the portion required for the determination of phosphatase has been removed, the test for urine must be made with small quantities of reagents. Since the proportion of urine is also often small, the colours are faint. This, in connection with the fact that no control test can be made with expressed secretion containing no creatinine, causes the greater accuracy which a reading from a photometer would give to be fictitious. Interpolation between the colours of the comparator test-tubes was made instead, and the results were converted into proportion of urine stated in per cent. The admixture of 2 mm^3 of urine to a system will in most cases cause a distinct change of colour, which means that it will be possible with certainty to detect a proportion of 20

per cent. of urine if the quantity of expressed secretion under examination is 10 mm^3, whilst a proportion of 4 per cent. is sufficient when the quantity of secretion is 50 mm^3.

It appeared in several recovery experiments that admixtures of urine could be determined with great accuracy, irrespective of the presence of a quantity of expressed secretion of up to 50 mm^3.

It seems to be of no real importance that no secretion is added to the comparator systems, as by far most test systems, irrespective of the admixture of secretion, have the same — yellow — colour as a blank system without any secretion. However, this does not apply to the presence of semen, which never gives a clear but an opalescent supernatant liquid and, further, always causes a red coloration. In the case of the samples in which, after admixture of picric acid and sedimentation, the upper liquid layer does not become limpid, we thus have to reckon with a considerable blank value. In such cases, which are of rare occurrence in examinations of expressed secretion, a reliable estimate of the proportion of urine is therefore impossible.

Determination of Admixture of Vesicular Secretion, if any.

The presence of vesicular secretion was ascertained by means of fructose which, as first demonstrated by Mann (1945) and Pryde (1946), is the only carbohydrate present in seminal fluid.

The method was prepared on the basis of the observation made by Jordan and Pryde (1938) that fructose, skatole and concentrated hydrochloric acid yield a cherry colour. The test is made in the following manner: A quantity not less than 10 and not exceeding 20 mm^3 of expressed secretion is run out of a pipette into a small test-tube to which are added 100 mm^3 of "cadmium sulphate solution" (composition: 34.667 gm of 3 $CdSO_4$, 8 H_2O+169.3 ml of $N/1$ H_2SO_4 made up with water to 1 litre; modified by Smith *et al.* (1945) after Fujita and Iwatake (1931)), and 100 mm^3 of 1.1/3 N sodium hydroxide solution. After vigorous shaking the mixture is allowed to stand for 15 minutes. Then it is centrifuged for 10 minutes at 2,500 revolutions per minute in an ordinary laboratory centrifuge, which produces a compact

adherent precipitate. The upper, always clear liquid is removed by means of a pipette and left for 1 week at 37° to dry up. A quantity of 50 mm^3 of a solution of 1 per cent. recrystallized skatole in absolute alcohol is then added (after preparation the solution is purified on activated carbon and kept in an ice-box; after it has been kept for 1 or 2 months it produces too intense a colour in blank test); further, 0.50 ml of concentrated hydrochloric acid solution is added. The dried-up precipitate is then stirred up vigorously with a spatula, and then suspension is allowed to stand for 30 minutes in water-bath at 37° C. The colour developed is then compared with the colours of blank systems (skatole alcohol+hydrochloric acid) and comparator systems that have been treated similarly but do not contain expressed secretion, but known proportions of fructose added in solid form, generally 5—10—25—50 gammas of fructose, prepared by evaporation in the tubes of adequate quantities of a 1 per cent. aqueous solution of fructose, preserved by means of chloroform and kept in an ice-box. If necessary, estimated interpolation is made between the colours of the comparator.

Comment on the Method.

The evaporation before the admixtures of skatole and concentrated hydrochloric acid is made to secure a purely red colour, as even minute quantities of water produce a colour resembling that of a permanganate solution. The faintest blank coloration is achieved with recrystallized skatole and can be further attenuated by purification of the alcoholic solution on activated carbon. Theoretically it may be objected that the blank system should contain expressed prostatic secretion minus fructose but as the great majority of expressed secretions develop colours which cannot be distinguished from that of the blank system, we may take it that the test is strictly specific of fructose among the substances occurring in expressed secretion. After admixture of pressed yeast to semen and a brief incubation at 37° C., skatole and hydrochloric acid also produce colours which cannot be distinguished from that of the blank system containing no semen.

Recovery experiments were made with semen by adding a quantity of yeast first, then incubating the mixture for a short period at 37° C.; this was followed by inactivation of the yeast

by heating to 100° C. and admixture of fructose. In such experiments the amount of fructose added was recovered quantitatively, which excludes the presence in expressed prostatic secretion and in semen of substances which might prevent the reaction of fructose with skatole.

The result is stated in gammas of fructose per 10 mm^3 of secretion. A correct conversion into the more expedient unit: "Admixture of vesicular secretion stated in per cent." cannot be effected, as it is only rarely possible to obtain unquestionable pure secretion from the seminal vesicles for comparison.

Pryde (1946) found concentrations from 290 to 400 m% in 3 fresh human ejaculates. Converted into pure vesicular gland secretion (estimated here at $^3/_4$ of the total volume of the ejaculate) it gives concentrations varying from 400 to 500 m%. These figures are in conformity with those observed by Huggins and Johnson (1933) but misinterpreted as representing glucose. In 4 portions of secretion expressed from vesicular glands they found from 275 to 625 m%, and in 9 ejaculates from 312 to 560 m%. In 150 ejaculates Harvey (1948) found concentrations of fructose from 5 to 640 m%, averaging 287 m% (see also page 46).

By means of the methods described here for the determination of fructose in expressed prostatic secretion the colour developed by 2 gammas of fructose can be clearly distinguished from the colour observed in the blank experiment, which again means that in 10 mm^3 of expressed prostatic secretion it is possible to ascertain the presence of a minimum admixture of one-fifth of vesicular secretion (with a content of fructose of 300 m%). When a quantity of 20 mm^3 of expressed prostatic secretion is examined and if the concentration of fructose in the admixture of secretion is 500 m%, it is possible to demonstrate at least one-fiftieth of admixture. The method is thus sufficiently sensitive for the purpose. Moreover, it is a specific method, as neither pure prostatic secretion nor the secretion of Cowper's glands in the proportions mentioned gives the colour reaction.

If an amount of more than 50 gammas of fructose is present in the system, the colour becomes too dark for even a rough interpolation to be made but, as has been calculated, the available range is quite sufficient for the purpose.

A total of 171 portions of expressed prostatic secretion varying from 10 to 20 mm^3 has been examined for fructose. Before the determination the samples are kept below 4° C.; in the writer's experience, and according to Mann (1946), no appreciable fructolysis takes place during the first few days at this temperature. The reaction was negative (i. e. < 1 gamma of fructose) in 152 cases.

In the remaining 19 cases the results were as follows:—

20 mm^3 contained 2 gammas of fructose: 5 cases
10 — — 1 to 2 — — — 8 —
10 — — 2 — — — 6 —

Neither in the 152 negative nor in the above-mentioned 5+8 cases did the consistency of the expressed secretion betray any admixture of vesicular secretion.

In the 6 last-mentioned cases the following portions were isolated by expression:—

(1) A serous portion (*a*) and a portion (*b*) of a gelatinous consistency.

(2) A serous portion (*a*) and a portion (*b*) of a moderately gelatinous consistency and containing vermiform "plugs" (microscopy showed spermatozoa) and, finally, a portion (*c*) which was of a markedly gelatinous consistency.

(3) and (4) The expressed secretion was of a gelatinous consistency. Duplicate tests were made in these cases.

In all these 4 cases the expressed prostatic secretion was liquefied when allowed to stand.

(5) The expressed secretion was brownish sanguinolent, of a watery consistency.

(6) The expressed secretion was mucous but not gelatinous, and did not liquefy when allowed to stand.

The expressed secretions contained the following proportions of fructose:—

(1) (a) 30 mm^3 contained 1.5 gammas of fructose
(b) 30 — — 40 — — —
(2) (a) 30 — — 0 — — —
(b) 10 — — 15 — — —
(c) 6 — — 10 — — —
(3) 10 — — 2 — — —
19 — — 5 — — —

(4)	10 mm³	contained	7	gammas	of	fructose
	20 —	—	13	—	—	—
(5)	30 —	—	10	—	—	—
(6)	18 —	—	4	—	—	—

These examinations show that vesicular secretion is only rarely expressed by massage of the prostate and also that, owing to its characteristic consistency, this secretion will be detected already when the expressed prostatic secretion is drawn up, provided the admixture is not very scanty (i. e. < 2 gammas of fructose per 10 mm³ of expressed secretion).

Both these conclusions become invalidated if the vesicular secretion is often free from fructose or often of a watery consistency already at the moment of expression. Mann and Parsons, in 1947, showed that after castration of bulls the production of fructose by the vesicular glands ceases, but continues under treatment with testosterone. As shown by Moore and Price (1938), a histologically normal prostate can be produced by doses of testosterone propionate which are lower than those required to produce histologically normal vesicular glands in animal subjects, and it is, therefore, possible that hypandrogenic individuals may have a testis hormone production which is sufficient to secure a normal production of phosphatase but insufficient for the stimulation of the vesicular glands which, therefore, give off a serous secretion containing no fructose.

It has been attempted to elucidate the problem by examinations of ejaculates of hypandrogenic individuals at the beginning and after cessation of treatment with sex hormones. The results are stated in Table VII and show that there are greater gaps in the concentration of fructose in the ejaculate than in its concentration of phosphatase. In Nos. 18 and 153 there are, however, no unquestionable signs showing that the production of fructose ceases earlier than that of phosphatase.

When the treatment is resumed, both the concentration of fructose and that of phosphatase are high in the first ejaculate. The mentioned irregular fall of the concentration of fructose may be due to either a decrease of the concentration of fructose in the secretion of the vesicular glands or a smaller proportion of the secretion in the ejaculate. The same applies to No. 165

Table VII

Phosphatase and Fructose in Ejaculates at Beginning and End of Treatment.

Date	Concentration of phosphatase in K.P.U.	Volume in ml.	Amount of phosphatase	Concentration of fructose
No. 18 (Eunuchoidismus postop.). See Figures 1 and 16.				
16/1-47	Discont. methyl testosterone (5 mg × 4).			
22/1	3.1	0.5	1.5	12
5/2	3.6	0.1	0.3	6
12	2.8	0.1	0.2	10
19	2.7	0.1	0.2	15
26	3.3	0.1	0.2	1
6/3	1.5	0.1	0.2	30
19	2.0	0.1	0.1	3
27	2.0	0.1	0.1	3
	No ejaculate in spite of several attempts.			
8/5	Rp. methyl testosterone 5 mg × 4.			
21/5	2.1	1.2	2.5	22
11/6	3.0	1.3	3.8	30
18	2.6	1.1	2.8	50
23/7	2.6	1.6	4.2	0
30	2.8	1.4	3.8	28
21/8	3.9	1.3	5.4	2
29	Ct. methyl testosterone 5 mg × 1.			
10/9	5.1	1.3	5.6	20
15/10	3.7	1.3	4.7	30
23	3.6	1.6	5.7	0
29	3.6	1.5	5.1	35
7/11	3.3	1.2	3.8	50
13	3.7	1.0	3.5	30
20	3.9	1.1	4.1	25
26	3.6	0.8	2.8	20
No. 130 (Aspermatismus).				
28/11-46	Rp. Physex 1500 I.U. × 3 weekly.			
22/1-47	1.3	0.9	1.2	20
29	5.4	1.0	5.3	15
5/2	12.8	0.1	1.1	0
12	6.3	0.4	2.3	30
19	4.8	0.5	2.4	50
No. 153 (Eunuchoidismus). See Figures 1 and 24.				
4/2-47	last injection of Physex.			
22/2	0.2	0.1	-	55
2/3	0.2	0.6	0.1	50
11	0.2	0.5	0.1	25
19	No ejaculate.			
22	Rp. Physex 1500 I.U. × 3 weekly.			
27	0.2	0.7	0.1	30
3/4	0.3	1.2	0.4	0
9	0.3	1.9	0.6	30
16	0.3	2.3	0.8	35
24	0.3	0.8	-	4
1/5	0.4	1.8	0.6	25
8	0.5	2.1	1.0	30
21	0.3	2.9	1.0	13
23	Ct. Physex 3000 I.U. × 3 weekly.			

Table VII (cont.)

Date	Concentration of phosphatase in K.P.U.	Volume in ml.	Amount of phosphatase	Concentration of fructose	
No. 153 (Cont.)					
28	0.4	2.5	1.1	15	
11/6	0.6	2.4	1.4	50	
18	0.4	1.7	0.6	30	
18	Discont. Physex.				
24/7	0.1	0.3	0.1	0	
31	0.2		0.1	0	
22	Rp. methyl testosterone 10 mg × 3.				
15/10	0.2	2.0	0.4	30	
21	0.2	2.5	0.5	2	
30	0.2	1.9	0.3	35	
15/11	0.3	2.2	0.6	20	
12	0.2	2.6	0.5	50	
12	Discont. methyl testosterone.				
11/12	0.1	0.2	0.1	30	
17	0.2	0.4	0.1	20	
14/1-48	0.1	0.3	0.1	20	
21	0.5	0.3	0.2	20	
5/2	0.2	0.2	0.1	25	
21	Rp. testosterone propionate 25 mg × 3 weekly.				
3/3	0.3	1.6	0.5	28	
No. 165 (Eunuchoidismus). See Figures 1 and 24.					
1/5-47	Rp. Physex 1500 I.U. × 3 weekly.				
8	0.4				(expressed secretion)
9	0.2	1.0	0.2	7	(ejaculate)
22	2.9				(expressed secretion)
5/7	Discont. Physex.				
28/8	Rp. Physex 6000 I.U. × 3 weekly.				
13/11	Discont. Physex.				
8/1-48	1.4				(expressed secretion)
15	1.1				(expressed secretion)
21	1.1	0.1	0.2	2	(ejaculate)
22	0.9				(expressed secretion)
29	1.3				(expressed secretion)
No. 170 Infantilismus primarius). See Figures 1 and 24.					
18/11-47	last injection of Physex.				
20	0.6				(expressed secretion)
23	0.8	0.2	0.2	20	(ejaculate)
27	0.6				(expressed secretion)
4/12	0.7				(expressed secretion)
6	Rp. methyl testosterone 5 mg × 4.				
30	Discont. methyl testosterone.				
15/1-48	Rp. methyl testosterone 5 mg × 4.				
4/3	Ct. methyl testosterone 5 mg × 8.				
1/4	1.4				(expressed secretion)
15	0.6	1.8	1.2	40	(ejaculate)
15	Discont. methyl testosterone.				
22	0.8				(expressed secretion)

The values stated in columns 2, 3 and 4 have been approximated to the nearest tenth.

(examined on January 21st, 1948), but the determinations of the concentration of phosphatase made simultaneously in expressed secretion obtained from this patient settle the problem: As the concentration of phosphatase is the same in expressed secretion and ejaculate, the low concentration of fructose in this case must be due to the ejaculate consisting of pure prostatic secretion. Such ejaculation of pure prostatic secretion occurs now and again, possibly caused by rapid cessation of the orgasm. The table shows still another example hereof (No. 130, examined on February 5th, 1947).

Conclusion:—

Although the series of cases produced is not sufficiently large to settle the question, the findings rather seem to indicate that there is no great difference between the influence of testis hormone giving rise to a production of phosphatase and the one causing production of fructose. There is thus hardly any reason to suppose that the expressed secretions which have shown a negative fructose reaction will include any containing fructose-free secretion of the vesicular glands, apart from expressed secretions of patients who have such a high degree of hypandry that their prostatic secretion does not contain phosphatase; in such patients, however, an admixture of phosphatase-free secretion from other genital glands will not give rise to erroneous conclusions.

(2) Measurement of Certain Sex Characters.

Measurement of the Volume of the Testes.

The thickness, width and height of each testis are measured by means of a sliding caliper the legs of which are approached to each other until the testes are nearly pressed together, which is controlled by bidigital examination. The thickness of the scrotal reduplication outside the raphe scroti is also measured by means of the sliding caliper. An approximate expression of the volume of the testis is found by substituting in the following manner the values in the formula for the volume of an oblate ellipsoid: $4/3\ \pi\ ab^2$, where a and b are, respectively, the longer and the shorter axis.

Measurement of the Dimensions of the Penis.

The length of the free, non-erected penis, i. e. the distance

from the transition between the dorsum penis and the mons pubis to the tip of the glans, was measured. Further, the transverse diameter of the corpus penis was measured.

Estimate of the Growth of Pubic Hair and the Degree of the other Accessory Growth of Hair.

The individuals examined were classified both according to the intensity of the growth of pubes and according to the spread and intensity of the terminal hair (including the pubes) in the following groups:—

Pubes:—

0: Lacking pubes.
1: "Lanugopubes", i. e. fine, thin, short, non-pigmented, straight, close-set hairs just above the radix penis.
2: Very scanty pubes on a greatly reduced area at the radix penis.
3: Moderately dense pubes at the radix penis, or as a narrow border above the latter.
4: Dense and abundant pubes but on a reduced area.
5: Dense and abundant pubes on a normal area but sharply delimitated.
6: Dense and abundant pubes on a normal area, not sharply delimitated, with or without growth of hair along the linea alba.

Terminal Hair:—

0: Lack of pubes or lanugopubes.
1: Pubes, but no axillary hair or beard.
2: Pubes and axillary hair, but no beard.
3: Pubes and axillary hair. Frequency of shaving: once a week or at longer intervals.
4: Pubes and axillary hair. Shaving more than once a week.

A few of the individuals examined showed a deviation from the chronological sequence: pubes, axillary hair, beard, as Cases 16, 135 and 164 spontaneously developed a growth of beard of such an intensity that shaving was required before the growth of axillary hair began. This took place in Cases 18, 121 and 311 in the course of treatment with chorionic gonadotropin. In the classification of these 6 cases the growth of beard was considered, and the absence of axillary hair was left out of account. None of the individuals examined have had any growth of axillary hair or beard before the pubes had appeared.

Estimation of the Size of the Prostate.

According to the size and consistency of the prostate the individuals examined were classified in the following categories:—

0: The prostate impalpable, infantile.
1: Scarcely palpable.
2: Too small in height and not sufficiently prominent. Consistency soft or normal.
3: Normal size but of soft consistency.
4: Of normal size and consistency.

Estimation of Appearance of the Expressed Secretion.

The prostatic secretion is serous but according to the degree of hypandry it may be more or less cloudy. According to its degree of cloudiness, the expressed secretion is divided into four categories:—

1: Watery,
2: slightly cloudy,
3: cloudy,
4: milky.

Determination of the Excretion of Renal Hormones.

With regard to the method of analysis used, reference may be made to P e d e r s e n - B j e r g a a r d and T ø n n e s e n (1948).

In Chapter XIX mention is made of 6 persons in whom the content of gonadotropic, androgenic and oestrogenic hormones in 48-hour urine was determined. The other hormone analyses in the present work have been made in 24-hour urine. The contents of gonadotropin, oestrin and andrin are stated in, respectively, rat units, mouse units and international units per 24 hours. In the case of gonadotropinuria, statements in mouse units have been converted into rat units according to the equation 2 M. U. = 1 R. U. As far as andrinuria is concerned, the results stated in cock's comb units have been converted into international units according to the equation 1 C. U. = 5 I. U.

Determination of the Development of the Carpal Bones.

As a criterion of the development of the bones, that of the centres of ossification in the carpus was chosen, as it is most differentiated there. A certain "carpal age" has been fixed for each roentgenogram after comparison with those reproduced in T o d d's "Atlas of Skeletal Maturation (Hand)", 1937, which contains a standard roentgenogram for each 6 months from

3/12 to 18 9/12 years (for the first year of life, however, an X-ray for each 3 months), a total of 40 roentgenograms. For those of the roentgenograms in the present series which showed a development between two of T o d d's consecutive standards, the carpal age was fixed between the "ages" of such two standards, i. e. at whole or half years. The slightest changes of the appearance of the carpus, and consequently the greatest uncertainty in fixing the carpal age, are met with in two ranges, namely from 14 3/12 to 15 3/12 inclusive, and from 17 9/12 years and on. This, however, does not influence the conclusions to be drawn in the following.

Chapter XI

CHOICE OF A CRITERION OF THE PRODUCTION OF PHOSPHATASE IN THE PROSTATE

On the basis of the exposition given in the preceding pages it will be discussed which measurable function of the production of phosphatase may be supposed to be most suitable as an indicator hereof and thus — as will be dealt with in fuller detail later — of the production of androgens, especially that of testis hormone.

The suitability of the following quantities will be analysed:—

(1) The concentration of phosphatase in the ejaculate.
(2) The amount of phosphatase in the ejaculate.
(3) The excretion of phosphatase in the urine per time unit, e. g. in the 24 hours.
(4) The output of phosphatase by the prostate per time unit, e. g. in the 24 hours.
(5) The concentration of phosphatase in expressed secretion.

re (1). The concentration of phosphatase in the ejaculate depends on the following factors: Its concentration in the prostatic secretion, the amount of prostatic secretion ejaculated and the proportion of secretion ejaculated from the other glands. It must therefore be considered rather an indirect measure of the faculty of the prostate to produce phosphatase. A reduction of this faculty will, for instance, not manifest itself in the concentration of phosphatase of the ejaculate if the amount of secretions of the other glands is reduced in the same proportion as the prostatic ejaculate. As shown by Lundquist (1947 c), it is possible to calculate both the amount of the prostatic secretion contained in the ejaculate and its

concentration of phosphatase, but one of the conditions of such a calculation is that the collection of the ejaculate is fractional, which can rarely be practised under clinical conditions.

The employment of the uncorrected concentration of phosphatase in the ejaculate as a criterion of the faculty of the prostate for producing phosphatase must be expected to lead to paradoxical results now and again. As pointed out on page 30, the vesicular glands of animals are more sensitive to a decrease of the production of testis hormone than is the prostate, and if this holds good in man, too, a slight decrease may produce a rise of the concentration of phosphatase in the ejaculate, as a decrease of the proportion contributed by the vesicular glands may be isolated. It may, however, be mentioned that Engberg *et al.* (1947) on the contrary found a decreased concentration of phosphatase in ejaculates of cryptorchids who just have a slightly failing production of testis hormone. As these authors do not state the volumes of the ejaculates, it is impossible to explain the discrepancy between their findings and the results which might be expected.

re (2). The amount of phosphatase in the ejaculate is a more suitable function, as it is independent of any admixture of secretions from other glands. The amount of phosphatase ejaculated is, however, determined by the motor function of the prostate. A constant output of phosphatase will give a varying amount of the enzyme in the ejaculate if the ejaculatory power of the prostate varies, and, conversely, an increased production of secretion need not manifest itself if the ejaculatory power remains constant. To this must be added that the amount of phosphatase is dependent on two functions of the prostate, namely the faculty for producing secretion and the faculty for imparting to this secretion a certain concentration of phosphatase.

The determinations according to (1) and (2) both require that the patient is able to ejaculate and are, therefore, inapplicable in the case of markedly hypandrogenic patients. The great majority of the patients examined with a view to the present work thus lacked the power of ejaculation.

re (3). Scott and Huggins (1942) have suggested the spontaneous 24-hour evacuation of the prostate in the lower

urinary tract as a measure of the production of androgens. As mentioned on page 37, this excretion in the 24 hours is minute, about 1 normal drop. Moreover, it will be difficult to decide by means of this method whether the spontaneous output of phosphatase is reduced or suspended, as no immaterial part of the acid phosphatase of the urine (from one-fourth to one-fifth) originates, not from the prostate, but from renal excretion of acid phosphatase. Further, the excretion of phosphatase by the prostate in the urine as well as in semen is determined by two factors, namely the amount of, and the concentration in, the secretion produced, as mentioned in re (2).

re (4). It would undoubtedly be more valuable to determine the amount of phosphatase produced during a given period than to measure — as with method 3 — the part of the production that is excreted from the gland during the period. However, a necessary condition for measuring the total secretory effect is that it is possible completely to evacuate the secretion from the prostate, or at any rate to evacuate it so that the gland has the same contents of secretion every time. It will not be possible to evacuate the secretion completely, either at ejaculation (see page 43) or at expression, which only as a rare exception removes more than 200 mm^3, and there is no possibility of determining the amount retained in the prostate.

re (5). A determination of the concentration of phosphatase in the expressed prostatic secretion has certain advantages over the methods mentioned above. It registers a single function, namely the power of the prostate to impart to its secretion a sufficiently high content of phosphatase, a function which must be supposed to be of essential physiological importance to the metabolism in the seminal fluid. In choosing this method we abandon the practically unattainable aim, which is a determination of the production per time unit (method 4), but gain the practical advantage that the method is applicable in almost all men, as it is possible to express secretion from almost all in whom the prostate produces secretion (cf. methods 1 and 2). Further, it is posible to ascertain beyond doubt the absence of a production of phosphatase (namely by control in the course of ensuing treatment with chorionic gonadotropin, see chapter XV), an advantage lacking in method 3.

The determination of the concentration of phosphatase in expressed prostatic secretion was therefore chosen as the principal method of examination for the purpose of the present work. It is discussed in fuller detail on page 100 to what extent the expressed secretion is identical with the prostatic secretion.

Chapter XII

APPLICABILITY OF THE CONCENTRATION OF PHOSPHATASE AS AN INDICATOR OF THE PRODUCTION OF TESTIS HORMONE

Among the demands which an accessory sex character must comply with in order to afford a suitable basis for the estimation of the actual production of testis hormone, the following may be mentioned:—

I) It must be as specific as possible with regard to the production of testis hormone.

II) It must be suitably sensitive to this production.

III) The values in normal and pathological cases should not overlap too much.

IV) The values should not from time to time display variations which are essentially greater than the fluctuations of the production of hormones.

V) It must be possible to give a quantitative statement of such a sex character, or to divide it in degrees.

VI) The time passing from a change of the production of testis hormone until the sex character adjusts itself at the new level must be short.

VII) It must be reversible.

It will be examined in the following to what extent the concentration of phosphatase complies with these demands.

I **The Specificity of the Production of Phosphatase.**

The influence of the following hormones on the production of the enzyme has been examined:—

Testosterone (testosterone propionate and methyl testosterone).

Chorionic gonadotropin (Physex Leo).

Equine gonadotropin (Antex Leo).

Thyroid hormone (tablettae glandulae thyreoideae).

Oestradiol monobenzoate.

The extragonadal androgen production.

EXPLANATION OF THE FIGURES
(Figures 1—24).

Where nothing else stated the following symbols mean:—	*Ordinate:—*
● The concentration of phosphatase*) in expressed prostatic secretion:	K. P. U. (/ml)
+ The concentration of phosphatase in ejaculate:	K. P. U. (/ml)
× Amount of ejaculate:	ml
■ Amount of phosphatase in ejaculate:	K. P. U.

Treatment with hormone preparations is indicated by means of curves; the injection preparations by means of stepped curves in which the height of the perpendicular sections is determined by the size of the single dose; the sublingual and peroral preparations are indicated by means of straight lines the rise of which is determined by the size of the twenty-four hour dose. Where it has been necessary out of regard to space to interrupt curve representing the treatment, the interruption is marked "Ct" (Continued).

The following terms have been used in the figures:—	*Total dose at end of treatment stated in:—*
Ph. for Physex Leo	1000 I. U.
A. for Antex Leo	1000 I. U.
Tstpr. for testosterone propionate	grammes
Mt. for methyl testosterone	„
Oe. for oestradiol monobenzoate	1000 I. B. U.
Ty. for tablettae glandulae thyreoideae	1000 T. U.

The injection of Perandren (testosterone propionate) crystallicum Ciba is indicated by perpendicular fully inked rectangles in which a height of ⅔ mm means 25 mg.

In all the figures showing the course of the concentration of phosphatase in time the lower normal limit for the expressed prostatic secretion of normal middle-aged men (5 K. P. U., see chapter XIII) is indicated by a dot-and-dash line: y = 5 K. P. U.

In cases where it has been impossible to obtain any prostatic secretion by digital massage before the treatment, this is shown by the curves representing the concentration of phosphatase beginning from the base line.

The dates have been plotted along the *abscissa*. Where out of regard to space the time marking along the abscissas has been shortened, the values of the concentration of phosphatase and the dates are connected by means of dot-and-dash lines.

*) In the present book "acid" prostate phosphatase is abbreviated: phosphatase. By concentration of phosphatase is understood its concentration in expressed prostatic secretion.

Testosterone: This was administered to 15 patients in all (Nos. 18, 36, 42, 48, 66, 69, 79, 133, 149, 151, 153, 165, 170 and 174 and No. 43, a case of surgical castration, which will be dealt with separately in another section).

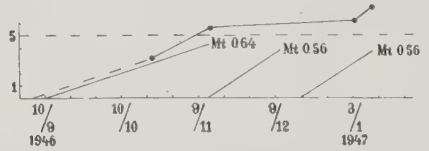
Figures 1 *a* and *b*.

Concentration of Phosphatase in the Course of Treatment with Testosterone.

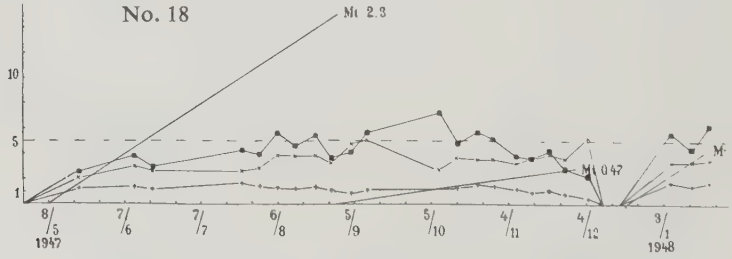
Methyl testosterone, indicated by oblique line.
Testosterone propionate, indicated by stepped curve.
Perandren crystallicum Ciba, indicated by rectangle.
Ordinate: concentration of phosphatase in K. P. U.

See also explanation in text, page 81.

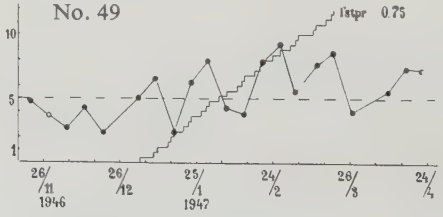
Fig. 1 *a*.



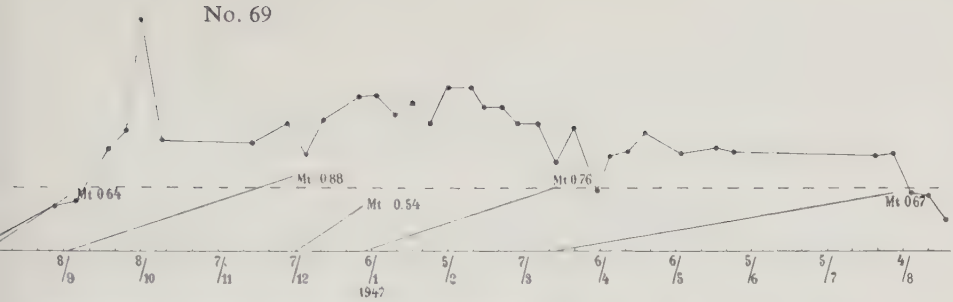
Daily dose of methyl testosterone, respectively 10, 20 and 20 mg



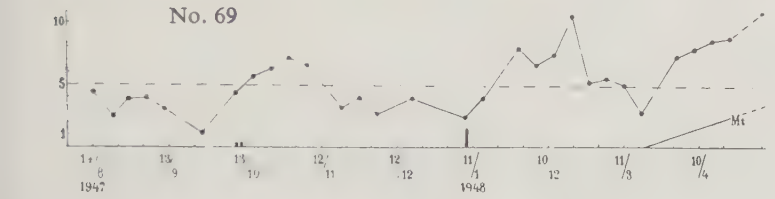
Daily dose of methyl testosterone, respectively 20, 5 and 20 mg
■—■ amount of phosphatase per ejaculate.
+—+ volume of ejaculate in ml.
×—× concentration of phosphatase in ejaculate.



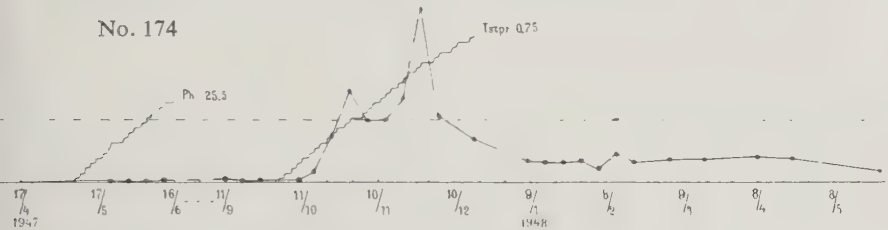
Single dose of testosterone propionate, 25 mg



Daily dose of methyl testosterone, respectively 20, 10, 20, 10 and 5 mg



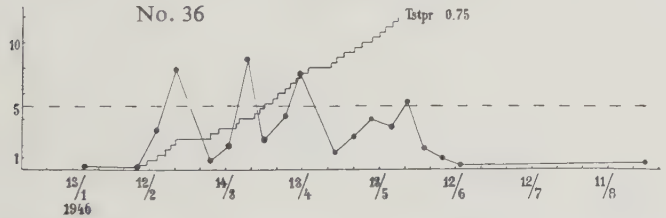
Perandren cryst. Ciba, respectively 25, 25 and 100 mg
Daily dose of methyl testosterone, 10 mg



Single dose of Physex Leo 1500 I. U.
Single dose of testosterone propionate 25 mg

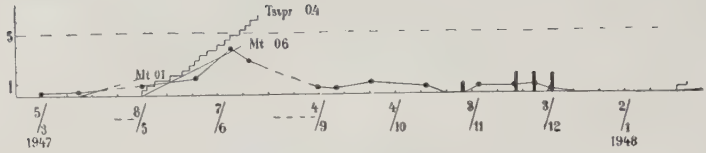
Fig. 1*a*: Four patients (Nos. 18, 49, 69 and 174) in whom testosterone increased the concentration of phosphatase to normal values.

Fig. 1 *b*.

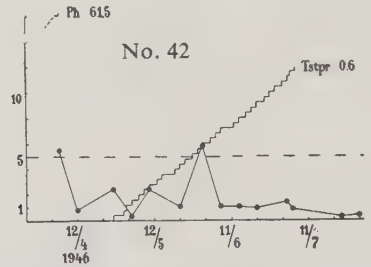


Single dose of testosterone propionate, 25 mg

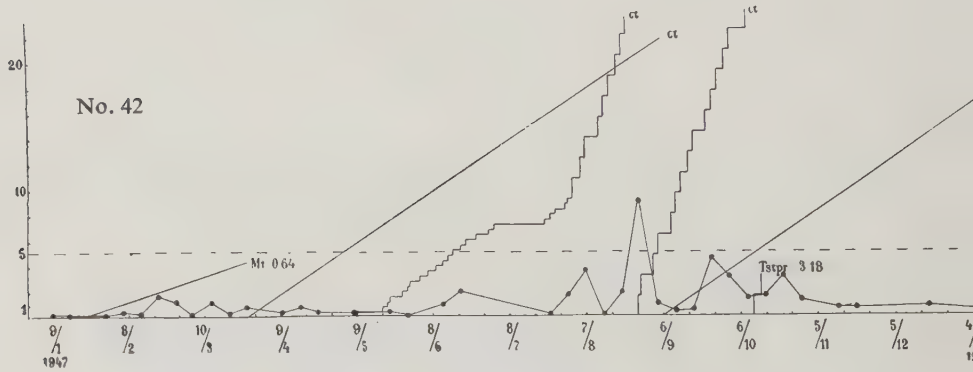
No. 36



Daily dose of methyl testosterone, respectively 5 and 5 mg
Single dose of testosterone propionate, 25 mg
Perandren cryst. Ciba, respectively 50, 100, 100 and 100 mg

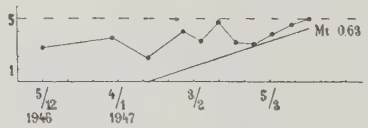


Single dose of testosterone propionate, 20 mg

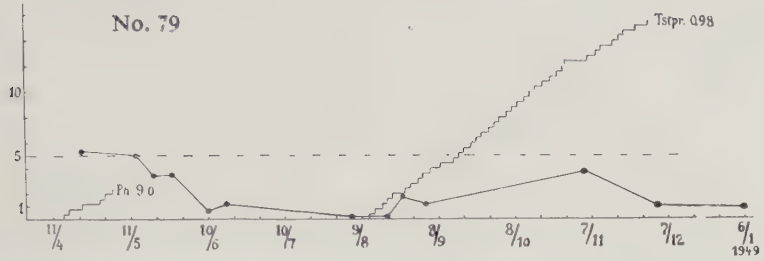


Daily dose of methyl testosterone, respectively 10 and 20 mg
Single dose of testosterone propionate, respectively 25 and 100 mg

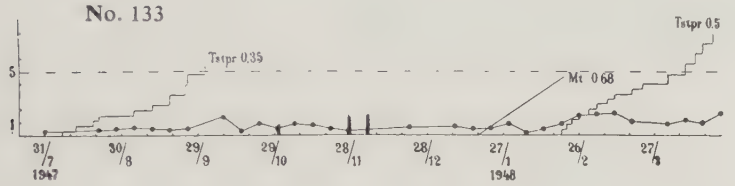
No. 66



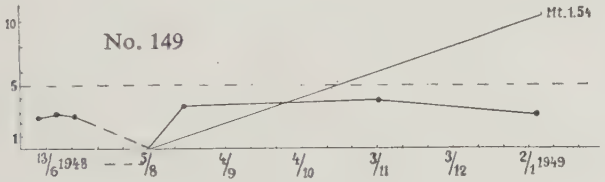
Daily dose of methyl testosterone, 10 mg



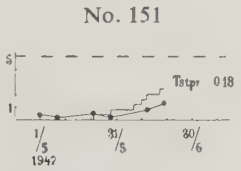
Single dose of testosterone propionate, 25 mg



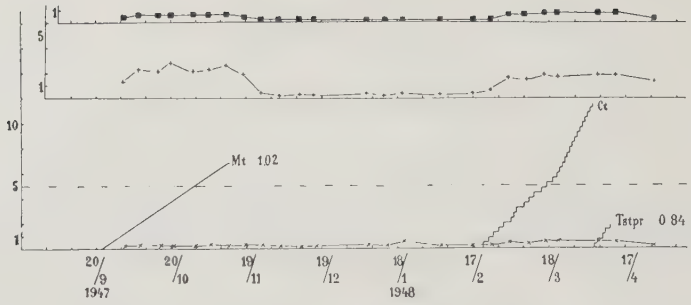
Single dose of
testosterone propionate, respectively 25 and 50 mg 25 and 50 mg
Single dose of Perandren cryst. Ciba, respectively 50, 100 and 100 mg
Daily dose of methyl testosterone, 20 mg



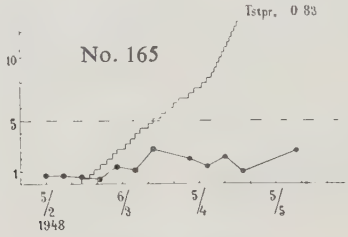
Daily dose of methyl testosterone, 10 mg



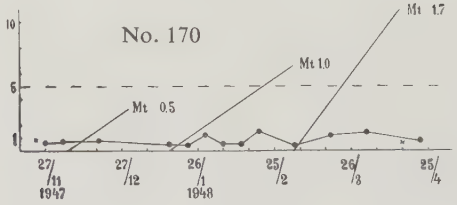
Single dose of testosterone propionate, 25 mg



Ordinate of **upper** curve: amount of phosphatase per ejaculate.
Ordinate of **middle** curve: volume of ejaculate.
Ordinate of **lower** curve: concentration of phosphatase in ejaculate.
Daily dose of methyl testosterone, 20 mg
Single dose of testosterone propionate, 25 mg



Single dose of testosterone propionate, 25 mg



Daily dose of methyl testosterone, respectively 20, 20 and 40 mg

Fig. 1*b*: Ten patients (Nos. 36, 42, 66, 79, 133, 149, 151, 153, 165 and 170) in whom testosterone increased the concentration of phosphatase to subnormal values.
The treatment of No. 151 was too brief. In No. 153 (ejaculate) the volume increased considerably, the concentration of phosphatase only slightly so.

The results were different, see Fig. 1. In Nos. 49, 69 and 174 a normal concentration of phosphatase, i. e. > 5 K. P. U. in the expressed secretion could be produced (Fig. 1 *a*), 5 K. P. U.

having been fixed as the lower limit of the concentration of phosphatase in normal, middle-aged men, see chapter XIII. In No. 18, treated with several series with intervening pauses, the ejaculate became normal every time as far as the concentration of phosphatase was concerned. A preceding treatment of this patient with chorionic gonadotropin + testosterone propionate produced a normal concentration of phosphatase in the expressed secretion.

In No. 49 an immediately preceding treatment with chorionic gonadotropin was capable of increasing the concentration of phosphatase to about 5 K. P. U., but the ensuing treatment with testosterone propionate took the values into the normal range.

No. 69 responded clearly to small doses both of testosterone propionate and of methyl testosterone, and the variations in the concentrations of phosphatase are due to the varying doses.

The following patients all responded to testosterone with a production of phosphatase, but the concentration of the enzyme in the expressed secretion became subnormal only:— Nos. 36, 42, 79, 133, 149, 151, 165 and 170. The same applies to the concentration of phosphatase in the ejaculate of No. 153. All the cases mentioned here were treated with quite large doses (Nos. 66 and 149, however, only with 10 mg of methyl testosterone daily) for a sufficiently long time, except No. 151; this patient obtained a concentration of phosphatase of about 1 K. P. U. In No. 66 the concentration produced by means of chorionic gonadotropin was not increased any further by methyl testosterone in the (rather small) daily dose administered.

The fact that some hypandrogenic patients do not respond with a normal concentration of phosphatase to treatment with testosterone may be due to one of the following causes:—

(1) The dose of testosterone may have been suboptimal.

(2) The prostate may be incapable of responding with a normal production of phosphatase in spite of a maximum adequate stimulation.

(3) The presence or administration of another hormone in addition to testosterone is required to ensure a normal production of phosphatase.

re (1). On looking at Fig. 1 *b* it is quite obvious that small doses administered for too short a period cannot explain all

the cases in which a normal concentration of phosphatase has not been achieved.

Nor can the choice of the preparation be the cause of the insufficient effect. There is, of course, the possibility that methyl testosterone may be inactivated before the resorption, but testosterone was administered solely in the form of the methyl compound in only 4 out of the 10 cases with a submaximal response (Fig. 1 b). The patients were all instructed to place the "linguettes" sublingually.

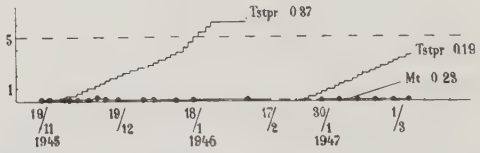
re (2). A course of treatment with testosterone in the case of surgical castration is an adequate therapy for the prostate. The writer has had the opportunity of following the expressed prostatic secretions before and during treatment with testosterone in such a patient (No. 43, Fig. 2), a man, aged 75, castrated at the age of 50 on medical indication (tuberculosis).

Figure 2.

Concentration of Phosphatase in the Course of Treatment with Testosterone Propionate in a Castrate in the Senium.

Ordinate: Concentration of phosphatase in K.P.U.
See also explanation in text, page 81.

No. 43



Single dose of testosterone propionate, respectively 10, 25 and 10 mg
Daily dose of methyl testosterone, 10 mg

The lacking production of phosphatase remained uninfluenced by testosterone.

He is the only patient of those examined in whom it proved impossible to start the production of phosphatase, even by means of large doses. It was not possible either to cause the prostate to increase in size; during the entire course of treatment it was quite infantile on palpation, and no unquestionable prostatic secretion could be expressed; judged by the creatinine analysis (see page 64) the expressed secretion chiefly consisted of urine. But the treatment exerted a distinct effect on the libido, which was revived; matutinal erections and increase of the body weight also occurred. This is the only case in which it has been ascertained beyond doubt that

the prostate was refractory to the adequate treatment. Whether the cause hereof is a physiological senile involution of the prostate, or too long a standing of the castrate condition (25 years), cannot be decided.

re (3). The assumption that the normal production of phosphatase is maintained by a combined influence of testosterone and another or several other hormones may explain the fact that some hypandrogenic patients do not obtain a normal concentration of phosphatase when treated with testosterone only.

Table VIII

Effect of Treatment with Testosterone on Concentration of Phosphatase (see Fig. 1) compared to Volume of Testes, Metabolism, Age and Diagnosis.

No.	Volume of testes in ml	Basal metabolic rate in per cent	Age	Diagnosis
Effect: normal concentration of phosphatase (see Fig. 1 *a*).				
18	< 1		19	Eunuchoidismus
49	about 2	122—106	16	Infantilismus primarius
69	< 1		24	Eunuchoidismus
174	about 2		12	Dystrofia adiposo-genitalis
Effect: subnormal concentration of phosphatase (see Fig. 1 *b*).				
36	2.8	87—85	22	Infantilismus secundarius
42	2.3	75—76	21	Infantilismus secundarius
66*)	about 2	92—91	16	Dystrofia adiposo-genitalis
79	1.0	97—107	21	Infantilismus secundarius
133	„ 1.5	66—61	13	Dystrofia adiposo-genitalis
149	„ 4.5		19	Pubertas tarda
151**)	about 2		14	Dystrofia adiposo-genitalis
153	about 5		34	Eunuchoidismus
165	about 5		37	Eunuchoidismus
170	4.7	98—102	15	Infantilismus primarius

*) Quite a low daily dose of methyl testosterone (10 mg)

**) Short period of treatment (1 month) and low total dose (175 mg of testosterone propionate)

Provided this assumption is correct, the difference between the patients who acquire a normal concentration of phosphatase in the course of treatment with testosterone and those who do not, may be that the former have a sufficient production of the — unknown — hormone in advance, which the latter have not. As 3 out of the 4 patients in the lower part of Table VIII displayed an initial lack of production of phosphatase, it may be concluded that the proportions of the hypo-

thetical hormone which are capable of augmenting the testosterone effect need not *per se* be sufficient to bring about a production of phosphatase.

In the patients whose provoked production of phosphatase is shown in Fig. 1 it has not been possible to correlate the response to testosterone with clinical data such as diagnosis, age, and the size of the testes (see Table VIII).

If the testes produce hormones of an effect exceeding the one that can be achieved by means of testosterone, a treatment with gonadotropin must be expected in some cases to produce a higher concentration of phosphatase than can be effected by a treatment with testosterone.

Chorionic gonadotropin was administered to 9 out of the 10 patients who responded subnormally (Nos. 36, 42, 66, 79, 149, 153, 165 and 170 — see Fig. 24 — and No. 133). In the last-mentioned case the effect was slighter than after testosterone, but it may be that the total dose has been too low (27,000 I. U.). In 2 cases (Nos. 79 and 149) the effect was considerably greater. As already mentioned, the dose of methyl testosterone administered to No. 149 was presumably too low. In the remaining 6 cases the two hormones exerted the same effect on the concentration of phosphatase.

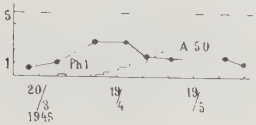
Equine gonadotropin was used for the following experiments: Four patients have been treated with this hormone (Nos. 8, 35, 36 and 49, see Fig. 3). None of these 4 patients displayed any increased production of phosphatase. In No. 8, who responded with a comparatively vigorous production of phosphatase to a few injections of chorionic gonadotropin, an ensuing treatment with equine gonadotropin could not prevent the fall of the concentration of phosphatase which set in after treatment with chorionic gonadotropin had been discontinued. In Nos. 35 and 49 whose concentrations of phosphatase had risen to subnormal values in the course of a preceding treatment with chorionic gonadotropin, no additional effect was achieved by equine gonadotropin. No. 35 later showed a vigorous, spontaneous rise of the production of phosphatase (see Fig. 24), and in No. 49 a higher concentration of phosphatase was produced by an ensuing treatment with testosterone. No. 36 responded with a normal production of phos-

Figure 3.

Concentration of Phosphatase in the Course of Treatment with Equine Gonadotropin.

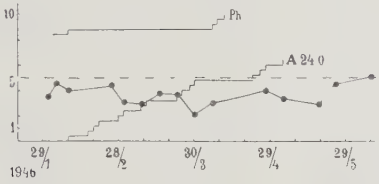
Ordinate: Concentration of phospatase in K.P.U.
See also explanation in text, page 81.

No. 8



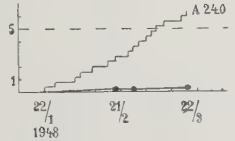
Single dose of Physex 300 I.U.
,, ,, ,, Antex 500 and 350 I.U.

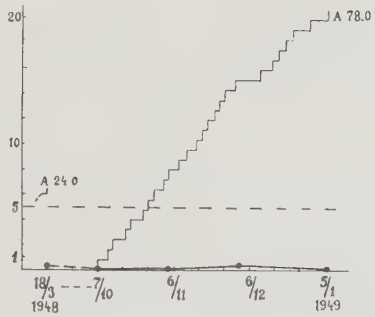
No. 35



Single dose of Physex 1500 I.U.
,, ,, ,, Antex 1500 I.U.

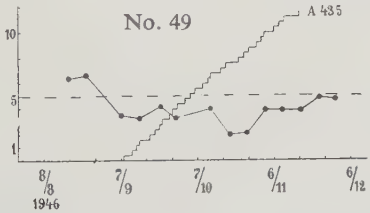
No. 36





Single dose of Antex 1500 I.U. 3000 I.U.

No. 49



Single dose of Antex 1500 I.U.

Four patients treated with equine gonadotropin. The production of phosphatase remained uninfluenced.

phatase in the course of a preceding treatment with chorionic gonadotropin.

It is impossible from this rather short series to give any decisive estimate of the effect of equine gonadotropin on the concentration of phosphatase, but these findings, compared with the almost inevitable effect of chorionic preparations on the production of phosphatase (see Fig. 24), are in good conformity with the animal experiments made by Engle (1932), Greep *et al.* (1936) and Greep (1939) who found that chorionic gonadotropin chiefly stimulates the Leydig cells of the testes, whereas equine gonadotropin largely promotes the development of the tubular cells. The last-mentioned authors also showed that chorionic, but not equine, gonadotropin exerts a stimulating effect on the prostate and the vesicular glands. Kemp *et al.* later found (1943) the same difference in the effect on the testes. On the basis of biopsies of the testes of men before and after treatment with chorionic, respectively equine, gonadotropin Heller and Nelson (1946) could corroborate the findings mentioned above.

The experiments with chorionic as well as equine gonadotropin reported above go against the view that the testes produce a hormone augmenting the effect of testosterone on the prostate.

Among the non-testicular hormones there are especially two to be considered in this connection, namely the adrenocortical and the thyroid hormones. The metabolism was thus examined in 5 out of the 8 patients with a subtotal response to testosterone, and was found to be lowered in 2 of these cases, see Table VIII.

The extragonadal Androgen Production.

Previous Investigators:—

Dorffman *et al.* (1948) have examined the androgenuria both photometrically and biometrically in monkeys which had been either gonadectomized or adrenalectomized, and in monkeys in which both the testes and the suprarenal glands had been removed. They found a fall of the excretion of 17-ketosteroids to about 50 per cent. a few days after a gonadectomy and a somewhat less decrease of the androgenic effect of the urine. After removal of the gonads as well as of the suprarenal

glands there was still an excretion both of 17-ketosteroids and of biologically active androgen amounting to about one-third of the normal, and the authors therefore presume that there is an extragonadal and extra-adrenal source (which is not supposed to be exogenous) of the androgen production.

In males suffering from cancer of the prostate with metastases Huggins and Scott performed similar double operations but could not demonstrate androgenuria afterwards (1945).

According to Fraser *et al.* (1941), the pathogenesis of many cases of the pituitary form of eunuchoidism includes a reduced function of the suprarenal cortex, presumably because the formation of the adrenotropic factor, like the production of gonadotropin, is impaired. In 12 patients suffering from eunuchoidism without increased renal excretion of follicle-stimulating hormone they found a lower excretion of 17-ketosteroids in the urine than might be expected even if the production by the testes had stopped completely.

The existing examinations of the renal excretion of androgens thus show that under normal conditions the organism is under androgen influence, not only from the testes but also from other endocrine organs, including at any rate the suprarenal glands. Further, the genesis of certain morbid hypandrogenic conditions seems to include not only a testicular but also an adrenal effect.

Writer's series.

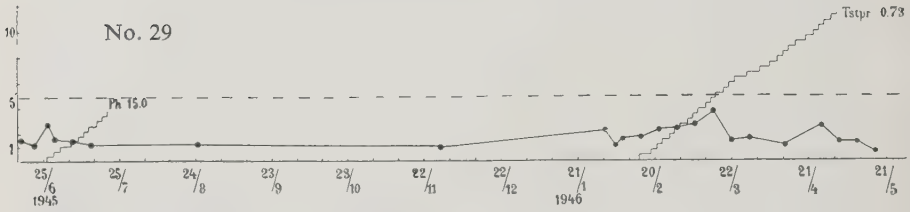
In hyperplasia of the suprarenal glands, which may produce pubertas præcox and virilism, it must be supposed in advance that a non-testicular production of phosphatase is kept up, which was also confirmed by the examinations of the following two patients, Nos. 29 and 139, Fig 4.

No. 29 is a female adrenal intersex whose rudimentary prostate because of the androgen production from the suprarenal glands had developed in the male direction to such a degree that the expressed secretion contained quite considerable amounts of phosphatase; up to 3.5 K. P. U. have been measured. An ejaculate showed a concentration of phosphatase of 1.1 K. P. U. The excretion of andrin in the urine was increased. Neither treatment with chorionic gonadotropin nor testoste-

Figure 4.

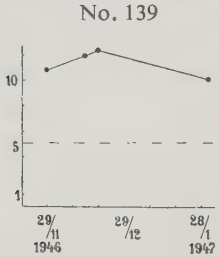
Concentration of Phosphatase in 2 Patients suffering from Hyperplasia of the Suprarenal Glands.

Ordinate: Concentration of phosphatase in K.P.U.
See also explanation in text page 81.



Single dose of Physex 1500 I.U.
Single dose of testosterone propionate, 25 mg
The concentration of phosphatase in ejaculate on Oct. 12th, 1946, was 1.1 K.P.U.

Female intersex, aged 20, suffering from hyperplasia adrenalis. The production of phosphatase remained uninfluenced by treatment with chorionic gonadotropin and testosterone propionate.
Her rudimentary prostate is capable of imparting to the secretion a certain concentration of phosphatase, but it is lower than the normal in a middle-aged man.



A boy, aged 3 years, suffering from pubertas præcox with hyperplasia adrenalis. The spontaneous concentration of phosphatase is within the range that is normal in a middle-aged man.

rone therapy could increase the concentration of phosphatase any further. The concentration thus represents the highest possible production of the rudimentary prostate of this patient.

The other patient, No. 139, was a 3-year-old boy suffering from pubertas præcox. In repeated examinations the concentration of phosphatase was of the same size as in normal, middle-aged men. The testes were very small, the size of nut-kernels, as is the rule in this disorder, and can hardly have been of any material importance to the prostate as compared to the suprarenal glands.

It proved impossible to procure extracts from the suprarenal cortex in sufficient quantities for the treatment of hypandrogenic patients. The question whether the adrenocortical hormones administered in physiological doses are capable of starting a production of phosphatase could therefore not be elucidated.

Thyroid hormone. — All the patients treated with this hormone had a lowered metabolic rate (Nos. 42, 79, 10, 133 and 180). Nos. 42 and 133 had been treated during another period with testosterone and responded to this with a subnormal production of phosphatase. No. 79 had responded with a normal production of phosphatase to treatment with chorionic gonadotropin. No. 101, who had a subnormal production of phosphatase for some unknown reason, was not myxoedematous or hypandrogenic. His low metabolic rate must presumably be considered a physiological variant. No. 180 suffered from myxoedema. His low concentration of phosphatase may, however, be due to an existing chronic prostatitis.

The production of phosphatase did not improve in any of the patients, see Fig. 5. The fact that, when administered alone, thyroid hormone does not influence the production of phos-

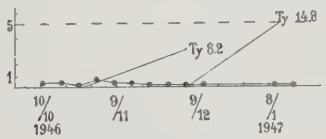
Figure 5.

The Concentration of Phosphatase in the Course of Thyroid Treatment.

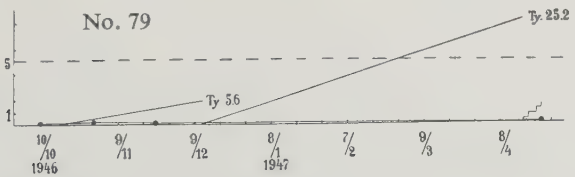
Ordinate: Concentration of phosphatase in K.P.U.

See also explanation in text, page 81.

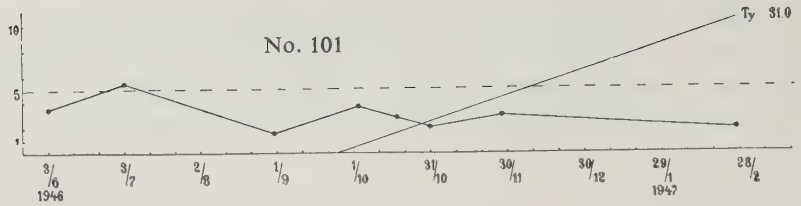
No. 42



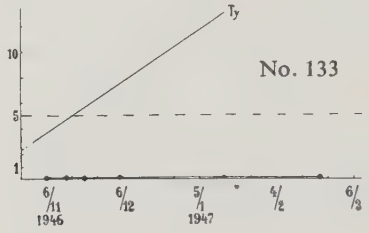
Daily dose, respectively 200 and 400 T.U.



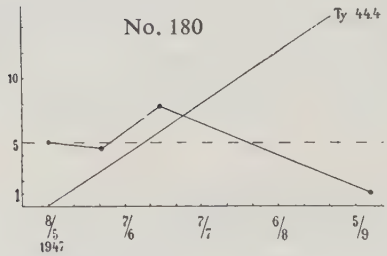
Daily dose, respectively 100 and 200 T.U.



Daily dose, 200 T.U.



Daily dose, 400 T.U.



Daily dose, 400 T.U.

Five patients treated with tablettae glandulae thyreoideae. The concentration of phosphatase remained uninfluenced.

phatase does not exclude that it may exert an augmenting effect on the stimulation of the prostate caused by testosterone. In 3 out of the 4 patients who gave a maximum response to testosterone (see page 87 and Fig. 1 *a*) the initial concentration of phosphatase was nil. The hormone which, as supposed hypothetically, should augment the action of testosterone thus exerts no effect itself on the production of phosphatase (see argumentation, page 89). The series does not include any cases treated simultaneously with thyroid and testosterone, but there is one case (No. 49, see Fig. 24) in which chorionic gonadotropin was administered simultaneously

with thyroid. On comparison with the effect of chorionic gonadotropin alone in this patient there seems to be a considerable augmentation in the combined treatment.

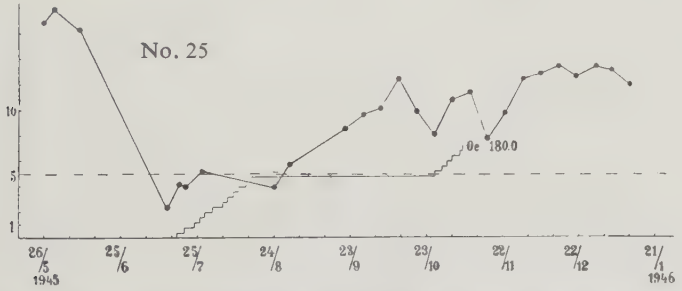
Lastly, 5 experiments made with oestradiol monobenzoate may be mentioned. It was used for the treatment of one patient who was not hypandrogenic (No. 56), 2 with impotentia coeundi (Nos. 30 and 116), a 65-year-old patient suffering from prostatic hypertrophy (No. 25), all the four patients with an initially normal concentration of phosphatase, and, finally, one eunuchoid (No. 7) who had a very low concentration of phosphatase in advance, about 1 K. P. U. The results, stated in Fig. 6, show that only in No. 25 there occurred a fall of the concentration of phosphatase, which fell from high normal values to about the lower normal limit in connection with the treatment; after it had been discontinued the values rose again. The decrease appeared already after the first injection (the analysis of the last expressed secretion before the treatment also showed a low value, but this result

Figure 6.

The Concentration of Phosphatase in the Course of Treatment with Oestradiol Monobenzoate.

Ordinate: Concentration of phosphatase in K.P.U.
Single dose of oestradiol monobenzoate: 10,000 I.B.U.

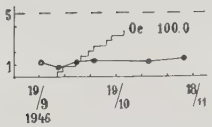
See also explanation in text, page 81.



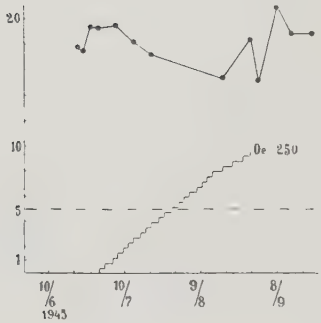
Doubtful result of the phosphatase analysis on July 13th, as most of the expressed secretion was lost.

A patient in the senium suffering from hypertrophy of the prostate. Doubtful whether treatment caused the fall of the concentration of phosphatase.

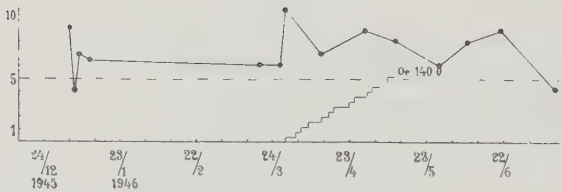
No. 7



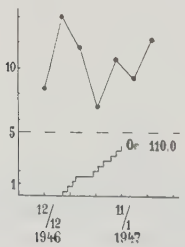
No. 30



No. 56



No. 116



Five patients treated with oestradiol monobenzoate. Doubtful effect on concentration of phosphatase in one (No. 25), no effect in the four.

is very questionable, as most of the secretion was lost) and it is therefore doubtful whether it is associated with the injections.

In the course of treatment Nos. 7 and 116 developed enlargement and tenderness of the glandular tissue of the breasts. The dosage and the duration of treatment have presumably been sufficient to preclude that a fall of the concentration of phosphatase would have occurred if the treatment had been prolonged.

Conclusion:—

Summing up, it may be said that testosterone (and chorionic gonadotropin through its influence on the testes) are the only hormones of those examined which in the doses employed can give rise to a production of phosphatase. In a number of cases the administration of testosterone produces a normal concentration of phosphatase, in others it becomes subnormal only, either because at that particular time the prostate lacks the power of producing a fully normal secretion in spite of adequate stimulation, or because the organism is deficient in other hormones required for a normal function of the prostate.

It may be pointed out here that the production of phosphatase is not the only accessory sex character that may respond insufficiently to treatment with testosterone. T a g e r (1942) found that a growth of beard in certain eunuchoids is produced with difficulty by this hormone.

II Sensivity of the Prostate to Testosterone.

In patients 18 and 69 a rough "titration" of the testosterone effect was attempted by means of the concentration of phosphatase. As shown by Fig. 1 *a*, a dose of 5 mg of methyl testosterone daily is sufficient in patient 69 to maintain a concentration of phosphatase about the normal range, and with 20 mg daily only a slightly higher value is produced. In No. 18 there is no unquestionable difference between the effect of 20 mg and that of 5 mg of methyl testosterone daily, either on the concentration or the amount of phosphatase in the ejaculate. The sensitivity thus varies to no small extent from one individual to another; thus No. 42 (see Fig. 1 *b*) responded only to very high doses.

III Overlapping of the Concentrations of Phosphatase in Normal and Hypandrogenic Individuals.

As mentioned in chapter XV the concentration of phosphatase comes into the normal range already at an early stage of sexual maturation and, consequently, mild degrees of hypandry cannot be diagnosed by means of the concentration of phosphatase.

IV Reproducibility. Examinations of spontaneous Variations of the Concentration of Phosphatase in Expressed Secretion on Repeated Expressions.

As will appear, *inter alia* from Table XVI, the concentrations of phosphatase in the two first expressed secretions of the same individual are generally found near each other, but differences which are not negligible are, however, seen now and again.

A similar inconstancy has been demonstrated by Lomholt *et al.* (1946).

The causes of these variations may be:—

(1) Errors in the determination.
(2) The admixture of other fluids to the prostatic secretion in the course of the expression.
(3) Variations in the composition of the actual prostatic secretion.

re (1). Errors in the Determination.

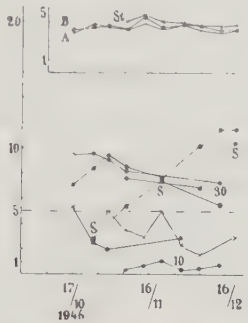
In order to estimate the reproducibility of the technique employed, the concentration of phosphatase was determined in the same two fractions of ejaculate (kept in a frozen condition) at intervals of one week during a period of 2 months. In the course of the same period the concentration of phosphatase was determined simultaneously in expressed secretions obtained at intervals of about a week from 7 individuals who were not or had not during the past 2 months been under treatment with hormones.

The results are stated in Fig. 7 and show that the variation in the analyses of the two samples of semen is decidedly less than the one found in the analyses of the expressed secretions; it is only slightly greater than in the recovery experiments made at the same time, in each of which a photometric determination of a constant, known amount of phenol was made.

Figure 7.

Variations of the Concentration of Phosphatase in repeatedly Expressed Secretions from 7 untreated Patients,

compared with the results of repeated analyses of 2 ejaculates (A og B) kept in a frozen condition between the analyses, and of a standard phenol solution (St). Twenty-six out of the 38 expressed secretions were examined for admixtures of urine. Positive reaction found only in 2 (marked 10 (= 10 %) and 30 (= 30 % of admixture of urine)). S: mucous expressed secretion.
Ordinates: Concentration of phosphatase in K. P. U.



The figures shows that the variations from time to time in the expressed secretions of an individual cannot be explained solely by the technique used in the determinations of phosphatase.

re (2). Admixtures of other Fluids.

Admixtures of the following fluids to the prostatic secretion may occur at the expression:—

(a) Urine,
(b) secretion from the vesicular glands,
(c) — — — testes, epididymes and the vasa deferentia,
(d) — — Cowper's glands.

Admixture of urine. — Before each expression the urethra has been "milked" and the external orifice has been wiped. Generally no urine can be expressed by this procedure. This does not preclude, however, that the walls of the urethra may be moistened with urine, and some may also be left in the pars posterior urethrae. Further, it cannot be considered out of the question that the internal orifice of the urethra may open and evacuate some urine from the bladder in the course of the expression which is almost always accompanied by an urge for micturition. The admixture of urine to the expressed

secretion has been examined according to the method described on page 64.

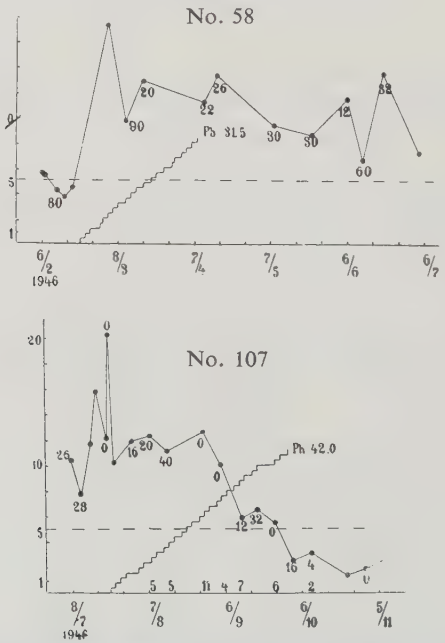
Twenty-six out of the 38 expressed secretions stated in Fig 7 were examined for admixture of urine. This was found in only 2 secretions. It can therefore be excluded as the cause of the variations of the concentration of phosphatase in this series. In some subjects, the admixture of urine may, however, be so frequent and so copious in the expressed secretions that it is impossible to get a reliable picture of the response of the

Figure 8.

Two Examples of a great Admixture of Urine and considerable Variations of the Concentration of Phosphatase.

Figures at curve: Admixture of urine in per cent.
Figures above abscissa: Intervals between preceding ejaculation and expression.
Ordinate: Concentration of phosphatase in K. P. U.

See also explanation in text, page 81.



The figures show that variations of the admixture of urine and intervals between ejaculations are not sufficient to explain the concentration of phosphatase.
The high percentages of admixture of urine may be fictitious, caused by a scanty admixture of other fractions of the semen, which, as mentioned on page 65, may give a red colour reaction with picric acid.

prostate to a given therapy. This applies, for example, to Nos. 58 and 107 (Fig. 8). However, the admixture of urine is insufficient to explain the variations of the concentration of phosphatase in these two patients.

Admixture of secretions from the genital glands other than the prostate. — It holds good of all these secretions that both their appearance and their consistency differ from those of prostatic secretion, and their presence will thus be discovered in the course of the expression and drawing into the capillary tubes. The unmixed serous prostatic secretion is drawn almost instantaneously into the tube, whereas the other secretions, which are mucous or viscous, pass into the tube only with difficulty, or not at all. Whilst the limpid, distinctly ropy secretion of Cowper's glands retains its physical properties when stored and, therefore, recurs in the capillary tubes as lumps or threads, the gelatinous secretion from the vesicular glands and the one containing spermatozoa will be liquefied by the enzymes of the prostatic secretions and become quite serous; therefore, it cannot be separated from prostatic secretion when run out of the pipette later.

In the course of the examinations it was soon realized that expressed secretions obtained during the first few hours after an ejaculation are often very mucous, or do appear to be serous but have a much lower concentration of phosphatase than secretions expressed after a long interval between ejaculations. Generally, expressions have therefore not been made until at least 18 hours after the last ejaculation. When this period is observed, it seems as if the variations cannot be explained by different intervals between the ejaculations, as shown by Fig. 9 (No. 114) in which the intervals between the ejacutions during the last part of the period of examination are stated.

Admixture of vesicular secretion was detected as described on page 65.

In the course of the expression the characteristic viscous secretion was not observed in any of the expressed secretions the concentrations of phosphatase of which are shown in Fig. 7; thus an admixture from the vesicular glands cannot be the cause of the variations either.

Figure 9.

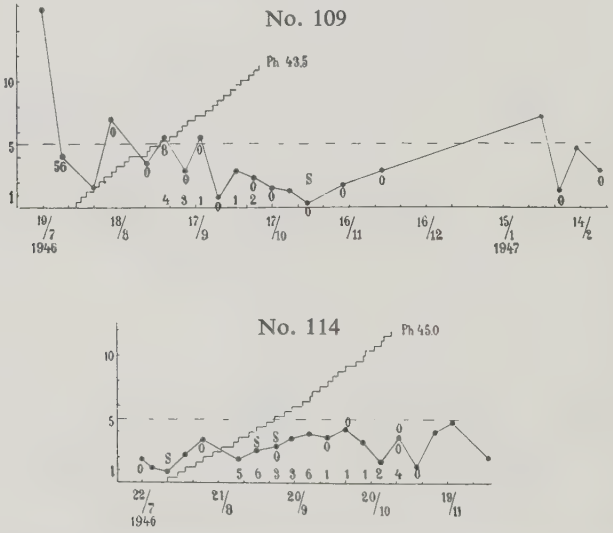
Other Examples of the Influence of

- **admixture of urine** (figures below the curve state admixture in per cent.),
- **admixture of secretion** of Cowper's glands (marked S),
- **interval between preceding ejaculation and expression** (figures above the abscissa state interval in days).

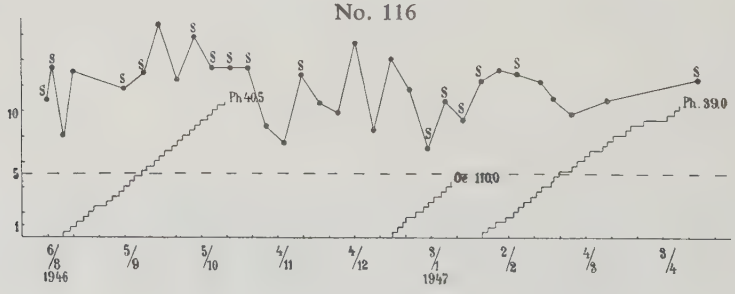
The 0's above the curve of No. 114 state the negative result of the fructose reaction.

Ordinate: Concentration of phosphatase in K. P. U.

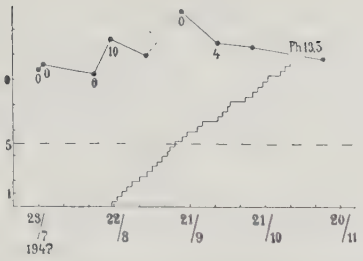
See also explanation in text, page 81.



Two patients with great variations of the concentration of phosphatase despite absence of admixture of urine.



No. 184



Two patients with a fairly constant concentration of phosphatase. In estimating these curves it has been considered that the standard deviation of the duplicate determinations rises in direct ratio to the concentration of phosphatase in the expressed secretion. The logarithm of the concentration of phosphatase of the various expressed secreations is more constant in Nos. 116 and 184 than in Nos. 109 and 114.

Secretions from the testes, epididymes and vasa deferentia can be revealed by the demonstration of spermatozoa in the expressed secretion. Twenty-seven expressed secretions chosen at random were examined microscopically, but no spermatozoa were found and, therefore, an admixture from the excretory ducts of the testes can hardly have been the cause of the variations. The proportion of expressed spermatozoa-free secretion from the vas deferens without any admixture of secretion from the testes-epididymes may be supposed to be negligible.

The secretion from Cowper's glands ("first drops", pre-ejaculatory secretion) will always be disclosed by its mucous consistency. These mucous masses can often be avoided either when drawing the secretion into capillary tubes or later when it is run out of the pipette. The expressed secretions which were of a non-serous consistency have been provided with a special mark in Fig. 9, but no correlation between the admixture of mucus and the concentration of phosphatase is observed.

In some subjects the admixtures of mucus occur frequently, a fact that will increase the variations of the concentration of phosphatase further, such as, for example, in No. 116 (Fig. 9).

re (3). Variations in the Composition of the actual Prostatic Secretion.

According to this the variations must be supposed to be due to changes of the concentration of phosphatase in the prostatic secretion itself. The changes hereof during the expression may

be imagined to be caused by the secretion of the terminal portions being diluted with water, or with secretion not containing phosphatase, in a varying proportion whilst it passes through the excretory ducts of the gland. If this is so, we must expect a lower concentration of phosphatase in the portion first expressed and a higher one in the portion last expressed, whilst the reverse would mean that an inspissation of the secretion of the terminal parts takes place in the excretory ducts.

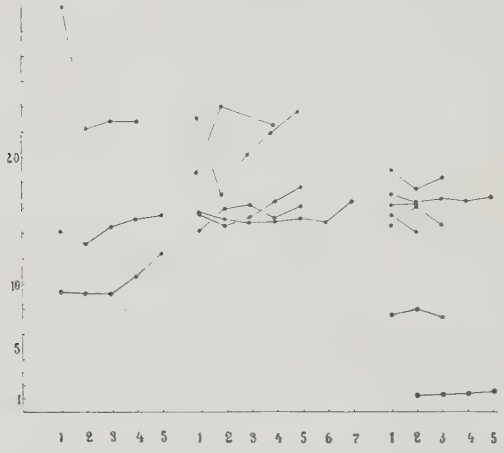
It was examined by means of two methods whether this took place:—

(A) A number of expressed secretions were secured in frac-

Figure 10.

The Concentration of Phosphatase in 15 expressed Secretions collected in up to 7 Fractions.

Ordinate: Concentration of phosphatase in the fractions, stated in K. P. U.
Abscissa: Sequence of fractions in one expressed secretion.



In a few expressed secretions a great arithmetical variation is seen in the concentration of phosphatase of the various portions.
Most of secretions, however, display almost the same concentration of phosphatase in the various portions.

tions, and the concentration of phosphatase was determined in the successive fractions. The results, reproduced in Fig. 10, show that, apart from a few of the expressed secretions in which a considerable, unsystematic variation is found between the concentrations of phosphatase of the fractions, there is no

significant difference between the contents in the various fractions of the same expressed secretion. It may be pointed out that the volume expressed constitutes a small part of the total content of secretion of the gland, so that it is possible that the experiment only tells something about the ratio between the concentrations of phosphatase in the secretion of the large excretory ducts and in that of the smaller ones.

(B) In 286 of the expressed secretions, one or more air vesicles were interposed in the capillary tubes separating the first and the last portions expressed; further, only the first and the last 10 mm^3 of the column of liquid were examined. It appears from Table V, Group 1, which does not include the 41 expressed secretions in which the concentration of phosphatase is < 1 K. P. U., that — compared with the determinations in mixed expressed secretions — a considerable difference between the concentrations of phosphatase in these two fractions is not infrequent. These differences are equally frequent whether the concentration of phosphatase is high or low, and an enumeration of this series shows that the concentration of the first fraction in 131 cases was higher and in 140 cases lower than that of the last fraction, whilst in 15 cases it equalled the concentration of the last fraction. If only the expressed secretions are considered in which a creatinine examination has shown the absence of admixture of urine, the figures are, respectively, 66, 60 and 4.

This "chance" evacuation of prostatic secretion goes against a dilution or an inspissation in the large excretory ducts and seems to indicate that the secretion from different portions of the prostate has a different concentration of phosphatase, and that in some cases evacuation takes place first from a portion of the gland with a secretion rich in phosphatase, in others from a portion containing secretion which has a low content of phosphatase.

The only paper published so far on the production of phosphatase in the various portions of the human prostate is that of Gomori (1941), who by means of a special histological technique has demonstrated the distribution of the acid phosphatase in tissue sections. He wrote as follows on the prostate phosphatases: "... the distribution of the enzyme is not uniform throughout the organ. The lateral and ventral

portions of the gland usually contain more enzyme than the dorsal portion. This applies both to man and the dog. Even within positive areas, scattered negative glands can be seen among a majority of positive ones. By staining consecutive serial sections with routine stains and for acid phosphatase, respectively, it was found that the positive do not differ morphologically from the negative glands".

Later, in 1947, Gomori wrote: "... There does not seem to be much difference in the phosphatase content between the lobes; instead, the peripheral portions of all lobes contain much more enzyme than the more central ones. It is mainly in these control areas that negative glands are found in large numbers".

These findings can only explain the heterogeneity of the prostatic secretion with regard to the concentration of phosphatase if the "negative" areas of the gland also produce secretion. Gomori's paper of 1941 does not contain photographs of such areas, but later he wrote (1947): "Their epithelial lining" (i. e. that of the negative glands) "is usually rather low; however, there are quite a number of well-developed true glands which are entirely negative or positive in a patchy way. Most of the negative glands are empty, but some of them contain positive secretions".

According to this, the cause of the, sometimes considerable, variations in the concentration of phosphatase in the expressed secretion from time to time may be supposed to be that the proportion of mixture between secretions from negative and positive areas changes from one expression to another.

It is striking that the inconstancy of the expressed secretions with regard to the concentration of phosphatase is pronounced only in certain individuals, e. g. in Nos. 109 and 114 (Fig. 9), whilst others display great uniformity, such as, for instance, Nos. 116 and 184 (Fig. 9). It seems as if Gomori can explain this by referring to the histological conditions (1947): "It seems that there is a considerable individual variation in the pattern of distribution of acid phosphatase in the prostate".

If the "negative" areas demonstrated by Gomori produce secretion, which seems probable according to the findings mentioned above, the concentration of the expressed secretion will be the resultant of a mixture of a phosphatase-free secre-

tion and one with a high content of phosphatase. If it is possible to convert these negative areas of the gland into positive ones in the course of a treatment with testosterone, the result will be a higher concentration of phosphatase in the expressed secretion.

Writer's Experiments:—

Two somatically fully virile men (Nos. 17 and 40) with impaired libido and impotentia coeundi and a patient suffering from slight eunuchoidism but with a normal concentration of phosphatase (No. 3, previously under treatment with gona-

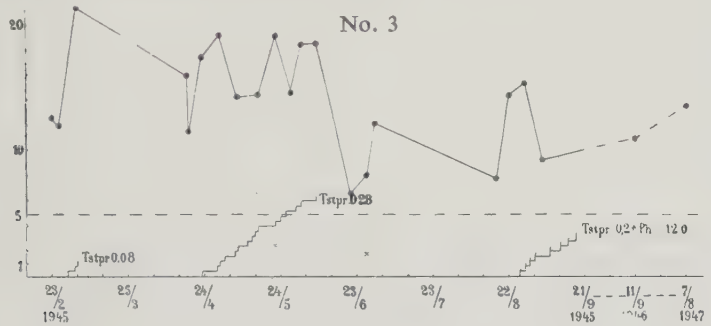
Figure 11.

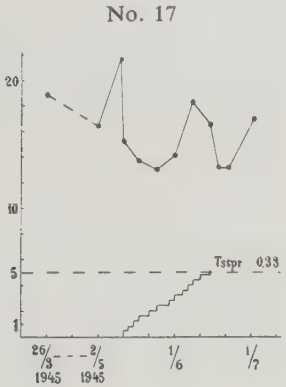
The Concentration of phosphatase in the Course of Treatment with Testosterone Propionate of 2 fully virile Men and 1 Patient with Eunuchoidism (No. 3), all with a normal Concentration of Phosphatase before Treatment.

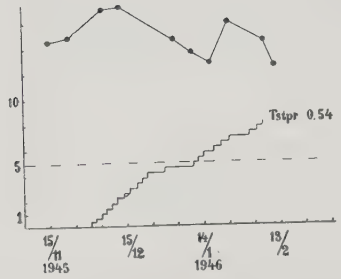
Ordinate: Concentration of phosphatase in K. P. U.

See also explanation in text, page 81.

Single dose of testosterone propionate: 25 mg







The production of phosphatase remained uninfluenced by testosterone propionate in 3 cases with a highly normal concentration of phosphatase in the expressed secretion before treatment.

dotropin) were given testosterone propionate for 1 to 2 months Fig. 11. Thus it could not be demonstrated that the presence in the prostate of secreting but negative areas is due to a supply of testis hormone which is suboptimal as far as these areas of the gland are concerned.

Mention may be made of another possibility in explanation of the variations of the concentration of phosphatase in the expressed secretions. It has been demonstrated by several authors, e. g. Gallagher *et al.* (1937), Hamburger (1948), and Pedersen-Bjergaard and Tønnesen (1948) that the andrinuria from day to day displays very great variations. If these findings are indicative of a varying production of androgens, it means that the adequate stimulus of the prostate varies from day to day. If, in the course hereof, the output of androgens now and again falls below the one required for a maximum stimulation of the prostate, the production of phosphatase must decrease. It cannot be said to how great an extent this fall will be compensated by the "air chamber" effect of the stored secretion.

V Unit of Measurement.

The concentration of phosphatase is stated in K. P. U. (for definition, see page 53) and always per ml of secretion. With respect to the reproducibility the following classification is sufficient in stating the intensity of the production of phosphatase in the individual case, the intensity being compared

with the one ascertained in adult midle-aged men (see chapter XIII):—

"0"	no production of secretion;
<1 K.P.U.	production of secretion but little or no production of phosphatase;
1- <5 —	subnormal production of phosphatase;
5- <10 —	low normal production of phosphatase;
≧10 —	high normal production of phosphatase.

This description of the level of the concentration of phosphatase will be used in the following when subjects are followed for a certain period with determinations of phosphatase. It proved to be expedient to use the following terms in addition:—

About 1 K. P. U.,
— 5 — — —

VI and VII Periods of Latency and Abatement of the Prostatic secretion. Reversibility.

It has been shown in the preceding pages that the production of phosphatase at any rate to some extent is due to the presence of a production of testis hormone in the organism, and that the concentration in the prostatic secretion may be increased — though not always — from 0 to normal values by the administration of testosterone preparations.

It has also been ascertained that among the hormones examined, only the testis hormones are capable of influencing the output of phosphatase if we do not consider conditions with a pathologicallly increased production of adrenocortical hormone.

The question is then whether the concentration of phosphatase indicates the actual production of testis hormone, or is a result of a testicular activity which has been present for a prolonged period in advance, in other words whether the prostate reacts quickly or slowly to changes of the intensity of its specific stimulus.

Previous Examinations (Animal Experiments).

(a) Course after Castration.

The bright areas in the alveolar-epithelial cells of the prostate of the rat diminish in the course of four days after castration (Moore *et al.*, 1930), but a stationary condition does not

appear until after 20 days. The effect on the cell-division in the prostate of the rat exerted by a single injection of testosterone propionate begins to subside after two days (Burkhart, 1939).

In guinea-pigs the involution after castration takes place quite slowly, is distinct after 10 and complete after 30 days (Sayles, 1942).

After castration of dogs the secretion of the prostate decreases within the first 24 hours and up to 3 weeks (Huggins and Johnson, 1933, Huggins and Clark, 1940) and after discontinuance of the treatment with testosterone in the course of 18 to 21 days.

(b) Latent period in the course of treatment with testosterone.

In old rabbits the size of the prostatic implant in the camera oculi anterior increases during the first 2 weeks of treatment with testosterone propionate, after which the growth ceases, or regression occurs, whereas the same treatment of castrated rabbits produces a constant growth for up to 3 months (Krichesky *et al.*, 1941).

After injections of testosterone propionate into castrated rats it is possible in the course of 24 hours to demonstrate an increase of the volume of epithelial cells in the ventral lobe of the prostate, accompanied by a mitotic division after 44 hours (Burkhart, 1939).

Complete restitution is only achieved after 20 days (Moore and Gallagher, 1930). When injected into immature dogs, the hormone produces a measurable prostatic secretion in the course of 3 to 7 days, with a constantly increasing secretion for at least 5 months (Huggins *et al.*, 1939).

Conclusion:— These experiments on animal subjects show that the latent period and the period of abatement of the secretory function of the prostate in animals during and after treatment with androgens only comprise some days.

Writer's examinations:—

The period passing from the institution of the treatment with testosterone to the time when the concentration of phosphatase in the expressed secretion shows a rise, respectively becomes constant, and the time passing from the cessation of the treatment to the beginning, respectively the cessation, of

the fall have been stated in Table IX. It shows that the latent period until the production of phosphatase is started does not exceed 1½ months, and that a stationary condition is established soon after the production of phosphatase has been increased during the treatment; further, that the time passing before the rise sets on is the same as the one passing before the fall begins, whilst the total periods of abatement show a greater variation.

To supplement this rather short series of patients treated with testosterone, Table IX also shows a number of cases treated with chorionic gonadotropin. In these cases the latent period comprises both that of the testes and that of the prostate, and in no small number of cases there will remain a production of phosphatase after discontinuance of the treatment because the hormone has stimulated the testes to a permanently increased output of androgens (see later). The production of phosphatase is thus indicative of an after-effect on the testes, not on the prostate. Actually, the series of cases treated with chorionic gonadotropin cannot therefore be used to invalidate the experiences with the testosterone therapy, but may possibly corroborate them.

This last-mentioned series shows that the latent period varies from about a week to several months, as a production of phosphatase begins after 3 months at the latest, but in the great majority of cases within 2 months after institution of the treatment.

An incipient fall and a new stationary condition after cessation of the treatment occur after a somewhat shorter period, so that the new stationary condition will have been established before 1 month in most cases.

It appears that the latent period is longer in the cases where the initial concentration is very low, or where no expressed secretion can be obtained. A shortened latent period is seen in case of repeated series of chorionic gonadotropin given in rapid succession. It will also be seen that the presence or absence of any initial expressed secretion does not influence the period of abatement (Table X).

A comparison between the series treated with testosterone and the one treated with chorionic gonadotropin shows that both the rise and the stationary condition begin a few weeks

Table IX

Latent Period and Period of Abatement of the Production of Phosphatase stated in Weeks during and after Treatment with Testosterone Propionate, respectively Chorionic Gonadotropin.

Duration in weeks

Concentration of phosphatase in K.P.U.	No.	Latent period: Incipient rise, at the earliest[1], at the latest[2]	Latent period: Stationary conditions, at the earliest[1] at the latest[2]	Period of abatement: Incipient fall, at the earliest[1], at the latest[2]	Period of abatement: Stationary conditions, at the earliest[1] at the latest[2]	
Testosterone (testosterone propionate or methyl testosterone)						
		[1] [2]	[1] [2]	[1] [2]	[1] [2]	
"0"	18*)	0 - 7	(expressed secretion)	3 - 6	6 - 6	(conc. of p.)
				0 - 1	6 - 6	(amount of p.)
		0 - 6	(—)	6 - 7	10 -12	(conc. of p.)
				2 - 3	10 -12	(amount of p.)
		0 - 2	0 - 2	1 - 1	1 - 1	(conc. of p.)
				1 - 1	1 - 1	(amount of p.)
		0 - 3	0 - 3			
	36	0 - 1	1 - 2	1 - 2	2 - 3	
		0 - 3	3 - 5			
	69	0 - 4	5 - 7	0 - 1	0 - 1	
	79	1 - 2	1 - 2			
	149	0 - 2	0 - 2			
	174	2 - 3	3 - 4	0 - 3	0 - 3	
< 1	**151**	**3 - 4**				
	165	1 - 2	1 - 2			
	153*)	0 - 1	0 - 1	1 - 2	10 -11	(conc. of p.)
				1 - 2	10 -11	(amount of p.)
Chorionic gonadotropin (first series which are followed by means of phosphatase analysis)						
"0"	36	1 - 2	3 - 4	1 - 2	2 - 3	
	49	12 -13	14 -15	2 - 3	4 - 6	
	68	0 -10	0 -10	1 - 7	1 - 7	
	70	7 - 9	7 - 9	No fall		
	79	8 -10	13 -15	0 - 1	1 - 2	
	97	4 - 5	8 -10	No fall		
	119	3 - 5	6 - 8	No fall		
	123	4 - 5	4 - 5			
	149	5 - 6	6 - 7	7 - 8	7 - 8	
	191	3 - 4	6 - 8	0 - 2	0 - 2	
	192	2 - 3	6 - 7	No fall		
	193	5 - 8	8 - 9	0 - 1	1 - 2	
	194	5 - 6	5 - 6	0 - 3	0 - 3	
	196	5 -10	10 -11	1 - 2	1 - 2	
< 1	7	1 - 4				
	35	3 - 5	5 - 8	No fall		
	42	2 - 3	2 - 3			
	54	5 - 6	5 - 6	1 - 2	1 - 2	
	55	1 - 3	1 - 3	2 - 3	2 - 3	
	126[0])	4 - 5	6 - 7	3 - 4	3 - 4	
	128	0 - 3				

Table IX (cont.)

	136	4 - 5	7 - 9	No fall			
	151[0])	4 - 5	7 - 9	No fall			
	165	1 - 3	1 - 3	0 - 4	0 - 4		
	170[0])	0 - 1	0 - 1				
about 1	8	0 - 2					
	134	0 - 3	5 - 7	No fall			
	189	1 - 2	4 - 5				
1- < 5	41	1 - 1	1 - 1				
	74	0 - 2	3 - 4	No fall			
	164	2 - 8	2 - 8	No fall			
about 5	12	0 - 1	2 - 3	9 - 9			
	153*)	0 - 1	6 - 7	0 - 5	8 - 9	(amount of p.)	

Repeated treatment with chorionic gonadotropin

						A	B
< 1	7	1 - 4					
< 1		0 - 4		No fall		9	
about 1	8	0 - 2					
< 1		0 - 1				3	
"0"	36	1 - 2	3 - 4	1 - 2	2 - 3		
< 1		4 - 5	5 - 6	2 - 3	3 - 7	10	5
"0"	49	12 -13	14 -15	2 - 3	4 - 6		
< 1		1 - 2	1 - 2	No fall		1½	
5- < 10		1 - 4	1 - 4			16	10
< 1	54	5 - 6	5 - 6	1 - 2	1 - 2		
< 1		0 - 2	0 - 2	0 - 3	0 - 3	2	
< 1		0 - 1	0 - 1	0 - 2	0 - 2	2	
< 1		2 - 3	2 - 3			12	
< 1	55	1 - 3	1 - 3	2 - 3	2 - 3		
< 1		0 - 1	1 - 2	1 - 3	1 - 3	1	
"0"	68	0 -10	0 -10	1 - 7	1 - 7		
about 5		0 - 4	0 - 4	0 - 2	0 - 2	2	
"0"	79	8 -10	13 -15	0 - 1	1 - 2		
"0"		1 - 2	6 - 9			7	
< 1	126	4 - 5	6 - 7	3 - 4	3 - 4		
"0"		9 -12				9	
"0"	149	5 - 6	6 - 7	7 - 8	7 - 8		
< 1		1 - 3	5 - 6	1 - 2	6 -10	3	
< 1		1 - 2	2 - 3	1 - 4	10 -15	3	
< 1	165	1 - 3	1 - 3	0 - 4	0 - 4		
< 1		1 - 2	1 - 2	2 - 3	11 -12	1½	
"0"	194	5 - 6	5 - 6	0 - 3	0 - 3		
< 1		0 - 2	0 - 2			1¼	

*) Ejaculate.

[0]) A preceding series treated with chorionic gonadotropin in which the concentration of phosphatase did not exceed 1 K.P.U. has not been included.

[1]) Time passing from the beginning (respectively discontinuance) of the treatment to the last day of examination before the rise (respectively stationary condition or fall) sets on.
[2]) Time passing from the beginning (respectively discontinuance) of the treatment to the first day of examination after the rise (respectively stationary condition or fall) had occurred.
A) Interval in months between the last treatment with chorionic gonadotropin and the present one.
B) Interval in months between the last treatment with testosterone and the present treatment with chorionic gonadotropin.

Table X

Patients with lacking initial Production of Phosphatase distributed according to Duration of latent Period and Period of Abatement in Connection with the first Course of Treatment with Chorionic Gonadotropin, followed by Means of Determinations of Phosphatase.

Number of Patients.

Concentration of phosphatase in K.P.U.	Duration	Latent period: Incipient rise, at the earliest[1]), at the latest[2])		Latent period: Stationary conditions, at the earliest[1]) at the latest[2])		Period of abatement: Incipient fall, at the earliest[1]), at the latest[2])		Period of abatement: Stationary conditions, at the earliest[1]) at the latest[2])	
		[1])	[2])	[1])	[2])	[1])	[2])	[1])	[2])
"0"	0-4 weeks	7	3	3	1	8	7	8	6
	5-8 — :	6	6	8	6	1	2	1	3
	9-12 — :	1	4	1	5				
	≧ 12 — :		1	2	2				
< 1	0-4 — :	10	6	4	4	4	4	4	4
	5-8 — :	1	5	5	3				
	9-12 — :				2				

[1]) and [2]), see legend for Table IX.

later after institution of the treatment in the latter series, presumably because the testes require a stimulation to increased production before any influence can be exerted on the prostate.

Conclusion:—

It will thus appear that the concentration of phosphatase ascertained in the expressed secretion at a given time is an indicator of the androgenic influence to which the prostate has been subjected within the 1 to 2 months preceding the expression, as an increasing supply of testis hormone will manifest itself more rapidly, the more highly developed the prostate is in advance. The production of phosphatase has

moreover appeared to be completely reversible, so that it will nearly always in the course of 1 or 2 months have adjusted itself according to a lower output of androgens. This means that the concentration of phosphatase in the expressed secretion at any time affords a picture of the production or the supply of testis hormone within the past 2 months. It may be mentioned that the time when the production of phosphatase begins or ceases, respectively rises or falls, must be prior to the moment when the concentration of phosphatase in the expressed secretion becomes stationary, as part of the expressed secretion obtained after discontinuance of the treatment may well have been formed at a certain, unknown, time in advance and then stored in the prostate, possibly diluted by secretion poor in phosphatase and produced later.

Chapter XIII

SERIES OF NORMAL CASES

The series of normal cases is divided into 3 groups: 13 individuals at ages from 13 to 19 years, 33 from 21 to 57 years, and 12 from 63 to 82 years; the last-mentioned group comprises no cases suffering from prostatic hypertrophy. The relevant data are shown in Table XI.

It may presumably be fitting to describe the sexually mature men first in the following reference to the series.

Normal middle-aged Men:—

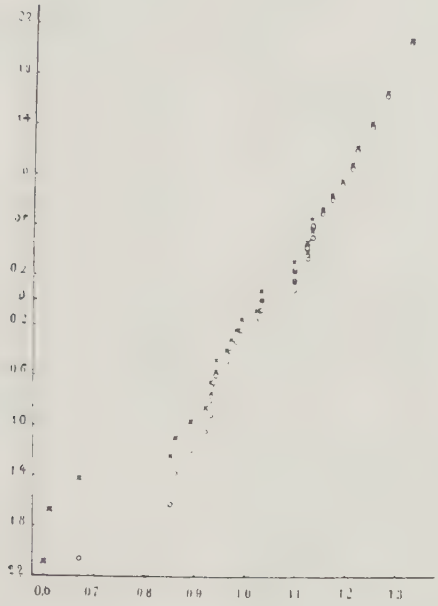
All the individuals examined were out of bed; libido, potency and somatic, accessory sex characters were normal. Five stated that they had previously been suffering from gonorrhoea. However, none of them now had any impairment of the urinary or genital tracts. One of the subjects had previously been affected with orchitis, but later had children of his own and has therefore not been left out of consideration. The size, shape and consistency of the prostate, and the appearance of the expressed secretion were normal in all subjects.

When plotted in a "rankit"-system (Ipsen and Jerne, 1944, and Fisher and Yates, 1938, Table IV), the arithmetical values of the concentration of phosphatase in the secretion first expressed show an arcuate course. On the other hand the logarithmic values show an approximately rectilinear course (Fig. 12), apart from the fact that the three lowest concentrations differ considerably. The following reasons suggest that the two lowest of the concentrations of phosphatase found should be left out of consideration in the normal series: The subject with the concentration 4.0 K. P. U. showed 9.8 K. P. U.

Figure 12.

The Concentration of Phosphatase in normal, middle-aged Men.

log concentration of phosphatase (abscissa) plotted in rankit system (ordinate).
×: 33 men.
o: 31 men (see text).



3 days later. The expressed secretion containing 4.2 K. P. U. was very mucous and inhomogeneous.

When these two values are left out, the others show a good rectilinear distribution, and the logarithms of the concentrations of phosphatase in this group can therefore be considered as being of normal distribution.

The characteristics of the series are shown in Table XII. The admixture of urine, if any, has been ignored in the computation on the following grounds: The presence of urine was found in 4 out of the 15 expressed secretions examined for this admixture. When correction is made for the content of urine determined, the arithmetical sum of the concentrations of phosphatase will be increased by 7.6 K. P. U..

If the admixture of urine is presumed to be as large in the other 16 expressed secretions not examined for urine, the mean

Table XI

Normal Series.

Concentration of Phosphatase (P_c) and other Properties in normal Boys under 20 Years (13 in all), Men between 20 and 59 Years (33 in all), and Men over 59 Years (12 in all).

Pc. in K.P.U. in: first expressed secretion	Pc. in K.P.U. in: second expressed secretion	log. Pc. in first expressed secretion	Admixture of urine in per cent in first expressed secretion	Excretion of Androgens in I.U. photometric estimation	Excretion of Androgens in I.U. biometric estimation
				Under 20 years.	
0.1	0.1		0		
1.2	1.4		3		
1.8	2.8		10		
3.6					
5.1					
6.6	9.6				11
7.0	10.7				5
9.7	10.7		0		
10.9					
13.4	6.2				23
13.9			0		
18.7					
19.9					
				Between 20 and 59 yea	
4.0	9.8	0.60	0		
4.2		.61		80	50
4.7	2.6	.67			
7.0		.85	0		
7.2	7.3	.86		35	45
7.7	4.7	.89	16		
8.3		.92			
8.6		.93	24		
8.6		.93	0		
8.7	11.8	.94	17		
8.8	10.8	.94		35	50
9.1	4.1	.96			
9.4	11.3	.97		110	65
9.6	12.5	.98	0	65	35
9.7		.99	0	135	135
10.5		1.02	0		
10.7	11.8	.03			
10.8	13.2	.03		15	10.5
12.2	6.8	.09		35	30
12.2		.09			
12.3	14.1	.09	0		
13.1		.12			
13.1		.12	0		
13.5	15.5	.13		45	30
13.6		.13	0		
14.2	14.9	.15	0		
14.7	9.0	.17		15	10
15.6	19.4	.19		130	160
16.2		.21	0		
16.5		.22			
17.9		.25	0		
19.0		.28	8		
21.3	18.4	.33		80	57

Volume of testes in ml	Ages	No.	Diagnoses and comments
12.4	13	150	Adipositas l. g.
18.5	14	187	Gynaecomastia in pubertate.
22.6	16	501	Asthma bronchiale.
28.1	16	502	Asthma bronchiale.
18.9	14	503	Asthma bronchiale.
9.9	13.6	127	Gynaecomastia in pubertate.
14.0	15	157	Nihil.
15.3	18	143	Nihil.
17.1	16	507	Asthma bronchiale.
15.2	19	504	Anxietas tibiarum.
28.2	16	505	Rhinitis vasomotorica.
20.8	17	169	Gastritis.
24.1	16	506	Asthma bronchiale.
		Gonorrhoea previously	
11.7	39	—	Asthma bronchiale.
23.3	47	—	Adipositas, sclerosis aa. coron.
	50	—	Thrombangiitis obliterans.
24.8	26	—	Asthma bronchiale.
21.8	50	+	Adipositas, angina pectoris.
27.8	42	+	Rhinitis allergica.
25.1	36	—	Asthma bronchiale, sinuitis.
28.0	41	+	Asthma bronchiale.
23.4	52	—	Asthma bronchiale.
24.9	34	—	Asthma bronchiale.
35.0	29	—	Gastritis, colitis.
	50	—	Thrombangiitis obliterans.
29.7	24	—	Gastritis.
13.8	21	—	Low stature, 167 cm.
21.4	29	—	Nihil.
11.8	53	—	Asthma bronchiale, orchitis antea.
19.3	37	—	Asthma bronchiale.
27.8	56	—	Gastroentero-anastom. facta.
17.4	21	—	Nihil.
	43	+	Adipositas, areflexia patellarum.
19.7	50	—	Asthma bronchiale.
23.3	36	—	Asthma bronchiale.
10.2	57	+	Angina pectoris.
27.7	41	—	Hypertensio arterialis l.g.
32.5	30	—	Asthma bronchiale, eczema.
21.7	30	—	Asthma bronchiale.
34.6	31	—	Neurosis cordis.
22.0	23	—	Gastritis.
36.0	38	—	Rhinitis allergica.
24.5	32	—	Asthma bronchiale.
16.1	55	—	Asthma bronchiale.
31.1	40	—	Asthma bronchiale.
17.7	21	—	Neurosis respiratoria.

Table XI (cont.

Pc. in K.P.U. in: first expressed secretion	Pc. in K.P.U. in: second expressed secretion	Admixture of urine in per cent in first expressed secretion	Excretion of Androgens in I.U. photometric estimation	Excretion of Androgens in I.U. biometric estimation
			60 years and older	
1.2	0.7		55	40
1.4	3.3		15	4.5
2.1	0.5	0		
2.9	2.6			
3.1				
3.7	4.2	0		
4.0		0	20	10
5.6				
5.7				
8.5				
11.7				
21.2				

Table XII

Concentration of Phosphatase.

Characteristics of Group 2, Table XI, i. e. normal Men between 20 and 59 Years.

	Number of persons	Mean figure (log concentration of phosphatase)	*s*	Mean concentration of phosphatase	Mean concentration of phosphatase $\pm$ 2 X standard deviation
A	33	1.021 K.P.U.	0.177	10.5 K.P.U	4.7 - 23.3 K.P.U.
B	31 (2 left out, see text)	1.048 —	0.146	11.2 —	5.8 - 21.6 —

In 9% (A) respectively 3 % (B) of normal, middle-aged men the concentration of phosphatase is expected to be < 6 K.P.U.

In 3% (A) — 1 % (B) — — — < 5 K.P.U.

In <1% (A) — < 1 % (B) — — — < 4 K.P.U.

The lower limit of "normal" concentration of phosphatase is fixed at 5 K.P.U.

figure will be increased by about 0.5 K. P. U. Considering the variation which will manifest itself in the concentration of phosphatase of the individual subject, this correction is insignificant.

The lower limit of the concentration of phosphatase of a normal middle-aged man can thus be fixed at 5.8 K. P. U. when the two lowest values are not considered. If they are included in the series, the corresponding limit will be 4.7 K. P. U. Values below 5 K. P. U. will be considered decreased in the following.

Further, in a number of persons in the normal series chosen

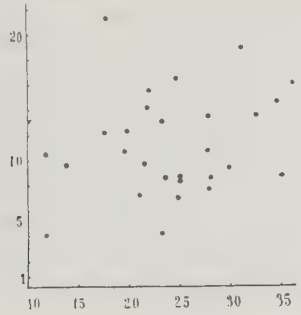
Volume of testes in ml	Ages	Gonorrhoea previously	Diagnoses and comments
24.5	71	+	Hernia inguinalis duplex.
17.0	77	—	Achylia gastrica.
24.3	65	+	Angina pectoris.
15.3	74	+	Epididymitis antea, Angina pectoris.
	82		
21.7	75	+	Lues antea, bundle-branch block, WR negative.
28.4	82	+	Sclerosis aa. coron.
	75		
	63		
	68		
	76		
	70		

at random, the **excretion of androgens** in 24-hour urine has been determined both photometrically and biometrically. It appears at once from the table that there is no unquestionable correlation between the concentration of phosphatase and the androgenuria in this series.

Lastly, the concentration of phosphatase has been compared with the **volume of the testes,** as shown in Fig. 13. In normal

Figure 13.

Relation between Volume of Testes (Abscissa) and Concentration of Phosphatase in K.P.U. (Ordinate) in 29 middle-aged, normal Men.



individuals there is no unquestionable correlation either between these two determinations. With regard to calculations of the volume of the testes, see Table XIII which shows that

in normal middle-aged men 25 and 10 ml can be fixed as, respectively, mean figure and lower limit for the volume of the testes, as these volumes may be considered as being of a normal distribution.

In normal middle-aged men a mean figure for the concentration of phosphatase from 10 to 11 K. P. U. and a lower limit of 5 K. P. U. have thus been found. The corresponding values for the volume of the testes are found to be 25 and 10 ml. No correlation

Table XIII

Volume of Testes.

Characteristics of Group 2, Table XI, i. e. normal Men between 20 and 59 Years.

Mean volume of testes	Standard deviation	Mean volume of testes $\pm$ 2 X standard deviation
23.5 ml	7 ml	9.8 — 47.8 ml.

can be demonstrated between the concentration of phosphatase on the one hand and the renal excretion of androgens, on the other hand.

Normal Adolescents:—

In the 13 normal pubescent individuals in whom secretion has been expressed, all values of the concentration of phosphatase were found. Values below 5 K. P. U. have not been found in 17-year-old or older individuals. Further, it may be mentioned that it proved impossible to express secretion from another 3 normal adolescents; they were all under 14 years, and in prepuberty or arriving at puberty. As they have not been subjected to treatment with hormones, it has not been possible to make sure that the absence of expressed secretion was tantamount to lacking production of phosphatase, cf. page 142. The three subjects have therefore not been included in Table XI.

This series is too small to decide whether the production of phosphatase during puberty is more closely connected with the age or with the somatic development, see Table XIX. The latter possibility is the more probable, as the production of phosphatase must be supposed in advance to follow the rule

applying to other sex characters which has been demonstrated by Greulich *et al.* (1942), see Chapter XVI.

Normal Individuals in the Senium.

Previous Investigators.

In the course of time a number of communications have been published which render possible an estimate of the decrease of the androgen production in the course of the senium. A decreasing libido, volume of the testes or spermiogenesis are not contributory with the certainty. According to Engle (1942), the degenerative changes in the course of the senium are not so marked in the testes as in the ovaries; Heller *et al.* (1941) and Hamilton *et al.* (1945) have not been able either to demonstrate a senile increase of the gonadotropinuria in man in contrast with their findings in woman. On the other hand, Österreicher (1934) found an increase of the prolanuria in one-fifth of all old men (but in all old women), and Hamburger and Halvorsen observed (1942) that 50 per cent. of all men over 60 years examined had a gonadotropinuria > 17 R. U./24 hours, an excretion found in three-fourths of castrated individuals examined. In 12 out of 14 middle-aged men gonadotropinuria was not demonstrated in the urine, in 2 the findings were, respectively, 17 and> 17 R. U./24 hours. Pedersen-Bjergaard and Tønnesen (1948) also found that the renal excretion of gonadotropin increases with advancing age, in particular after the sixtieth year.

According to Hamburger (1948), the excretion of 17-ketosteroids decreases after the age of 20 to 30 years, whilst the androgenic effect of the urine is reduced after the age of 30 to 40 years, and after the sixtieth year of life 24-hour excretions <20 I. U. frequently occur. Hamilton and Hamilton (1948) found a decreasing renal excretion of 17-ketosteroids, alpha-hydroxy- and beta-hydroxyketosteroids with advancing age in adult men. Pedersen-Bjergaard and Tønnesen (1948) also found that the androgenuria decreases with advancing age.

R. A. Moore (1936 *a*) found in histological examinations a presenile involution of the prostate in the sixth decade, as the glandular cells in some areas lose the secretory activity, changes which resemble incipient castration phenomena. This resemblance does not exclude that the changes are irreversible.

In microscopical examinations of (hypertrophic) prostates of old men operated on after a treatment with testosterone Moore and McLellan (1938) could not demonstrate unquestionable changes of the histological picture which might be attributed to the treatment.

The fall of the hyperphosphatasaemia after castration of aged patients with metastases from carcinoma of the prostate has been considered an indication that the testes of such patients, at any rate to a certain degree, produce androgenic hormones even in very old age. On the other hand, Burgen (1947) has found that the phosphatasuria, which is known to be due chiefly to the output of phosphatase by the prostate, displays an abrupt fall after the sixtieth year and becomes of the same magnitude as in women, which is also the case before the twentieth year, whereas between the twentieth and sixtieth years it is at a fairly constant, high level. This seems to indicate that normal prostatic tissue does not produce — at any rate does not give off to the urine — any phosphatase in the senium.

It is thus highly probable that the androgenic activity is reduced in men in the senium, but other findings also seem to indicate that it does not cease completely.

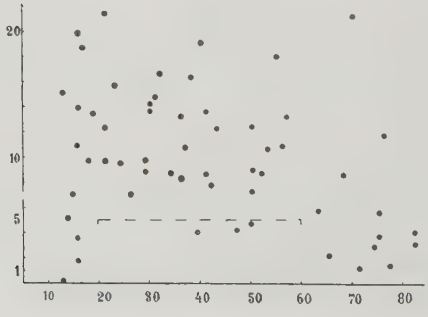
Writer's Series.

The fact that phosphatase may be present in expressed secretion from certain old men who are well on in the senium, as appears from Table XI and Fig. 14, is an incontestable proof

Figure 14.

Relation between Years of Life (Abscissa) and Concentration of Phosphatase in K.P.U. (Ordinate) in 57 Boys and Men.

(Normal Series, see Table XI)



that testis hormone must be produced to no small extent now and again even in old age. The fact that there are also many old men in whom the prostate does not produce phosphatase, or does so to a diminished degree only, does not mean that the production of testis hormone in these individuals has decreased or ceased. Only by following the concentration of phosphatase in expressed secretion in the course of treatment with testosterone — examinations which have not been included in the present work — it will be possible to decide whether the lacking production of phosphatase is due to a cessation of the production of testis hormone in these old individuals, or to a lack of response in the senile prostate; the latter possibility is supported by R. A. Moore's demonstration (1936 *a*) of the fact that during the senium the prostate inevitably undergoes degenerative, histologically demonstrable changes. It is striking to see that all the expressed secretions with a normal concentration of phosphatase (the lower 5 in Table XI, third section) have been obtained from inmates of "De Gamles By" ("The Old Age Pensioners' Town"), whilst all the decreased values have been found in outpatients. The series becomes less valuable because most of the latter category have been suffering from gonorrhoea and may therefore previously have been affected with prostatitis (see also page 45). In all these patients the prostate was, however, normal on palpation and none of them had had any postgonorrhoeal prostatic or urethral complaints, apart from the patient aged 74 who had been suffering from dysuria and swelling of the contents of the scrotum and whose prostate was small and displayed a single node. The determination of the production of phosphatase is particularly suited for the estimate as to whether the androgenic activity is impaired or not during the senium, because — in contrast with the other accessory sex characters — this function of the prostate is completely reversible (see page 113). The analyses made in this series show that the androgenic production is not infrequently retained, at any rate to some extent, through the senium, but that the concentration of phosphatase often falls to subnormal values.

Correlation between Concentration of Phosphatase and Age in Normal Individuals.

The values in all the normal individuals examined, a total of 58 from the thirteenth to the eighty-second years, are arranged according to age in Fig. 14. Low values occur at ages under 20 and over 60 years.

The dependence on age of the concentration of phosphatase is much the same as the one demonstrated by Hamburger and Halvorsen (1942) in the case of the renal excretion of androgenic hormones. The curve suggested by Hamburger (1948) representing the share of the testes in the 17-ketosteroid excretion (the difference between that of man and that of woman, chemically determined for each age-group) has its maximum in the fourth decade, just like Hamburger and Halvorsen's curve (1942) showing the excretion biometrically determined.

The curve showing the concentration of phosphatase (Fig. 14) follows a course resembling these two curves; its maximum appears, however, somewhat earlier, in the third decade, after which the values fall slowly until the age about 60 years, and then decreases abruptly. It may be mentioned that the sum of the share of the testes and the suprarenal glands in the 17-ketosteroid excretion is maximal in the third decade (Hamburger 1948).

Chapter XIV

HYPANDRY AND SEXUAL MATURITY. NOSOGRAPHIC CONSIDERATIONS

Hypandrogenic States.

The following is a survey of the considerations that led to the classification of the patients in the following series. In the preceding chapters, the term "hypandry" has been applied in a few instances; it will be used frequently in the following. "Hypandry", for the purpose of the present work, may be defined as a state in which the somatic sex characters have not reached a completely virile development, on account of an androgen production of a less magnitude than in normal adult men.

Thus every normal boy will, before and during puberty, exhibit a state of hypandry which is physiological, in that its degree is not abnormal for his age.

The opposite is "pathological hypandry", defined as a state of virile development subnormal for the person's age. In an adult man, ascertained hypandry would be of a pathological nature. During the years of puberty — generally considered to be between the ages of twelve and twenty — there are extremely wide limits to the degree of physiological hypandry: not until the ages of fifteen or sixteen may absence of the phenomena of puberty (e. g. non-appearance of the pubes) be taken as a symptom of pathological hypandry.

The problems of pathological hypandry during childhood will be dealt with in a subsequent section.

Diagnosing Pathological Hypandry.

There is no difficulty in ascertaining whether an adult male suffers from pathological hypandry. The symptoms are easily observed: too small, possibly soft, testes; low, flattened, and soft prostate; retarded or incomplete development of the pubes, hirci or beard; open epiphyseal lines; and, possibly, an eunuchoid appearance. Further, a childish voice, castrate's skin, psychoinfantilism, reduced libido, impotentia coeundi, aspermia, and, finally, reduced renal excretion of andrin. In the following the term a c c e s s o r y s e x c h a r a c t e r s will cover the functions mentioned above, with the exception of the size and consistency of the testes.

It is quite a different matter to establish the diagnosis of pathological hypandry in children in whom, among other things, no growth of terminal hair is present to facilitate our considerations. Only the conditions of the genitals may be taken as specific signs of an incomplete sexual maturity. At this age, there are no certain indications of pathological hypandry, apart from undescended testes or testes of an insufficient size, because it is difficult to ascertain a reduction of the infinitesimal quantities of androgen excretion, whereas deviations from normal growth and physique, and epiphyseal maturation, may well be pronounced, but are somewhat vague criteria for disturbances in the production of androgens.

As will appear from the following, it is a difficult question to decide whether the volume of the testes in children is reduced in proportion to their age..

As mentioned in Chapter XVI, a volume of the testes of 2 ml is abnormally small for a boy of 13 years or more. According to W i t h and F r o m H a n s e n's investigations, the lower limit of the normal volume of the testes appears to be about 1 ml under this age. By way of illustration, it may be explained that two spheres each with a diameter of 1 cm, would have a total volume of 1 ml. Possible errors in measuring such small volumes are considerable, among other reasons because the error in measuring the reduplication of the scrotum exerts a disproportionately great influence on the result. If made at all, the diagnosis "too small testes for a boy under 13", should be applied only if the testes are extremely small.

If the testes are found to be abnormally small, it does not

necessarily mean that the production of testicular hormones expected at a certain age, is reduced, because a diminished volume may result from a tubular hypoplasia. Finally, it appears that only a fraction of the usual number of Leydig cells is sufficient for the maintenance of normal sex characters.

Androgen Production in Childhood.

If the concept pathological hypandry in childhood is a reality, there must normally be an androgen production at the childish stage of development, and this production must, moreover, be sufficient to influence the accessory sex characters.

Certainly, a definite, inconsiderable growth of the sex organs takes place during the first ten years of a boy's life; thus, the weight of the prostate is doubled; the penis grows slightly longer and thicker; finally, the epiphyses mature. As, however, the growth of the sex organs during this period is proportionately smaller than the total increase in volume of the individual, it can hardly be considered a definite sign of androgenic effect.

Features worth examining for the further elucidation of these problems are, for example, the growth of the body maturing of the epiphyses, and the renal excretion of hormones, in particular gonadotropin, since a hyperexcretion of gonadotropin might indicate a cessation of the production of testicular hormones. Examinations of children with gonadal aplasia would scarcely afford reliable results, as the concurrent existence of some disturbance of development, independent of the aplasia, cannot with certainty be excluded. This applies to the cases of congenital ovarian absence or insufficiency reported by Pich (1936) and Albright, Smith and Fraser (1942). The best results could be obtained from investigations of prepubescent boys castrated at an early age but, to my knowledge, no report of this nature is available. Among the eunuchs examined by Wagenseil (1927 and 1933), several had been castrated during childhood, but examinations were performed at adult age. It is true that Bilharz (1860) examined two child eunuchs, but he reported on the state of their genitals only.

Whilst it has not yet been settled whether children have an androgen production which effects the development, conditions

are different after the age of ten, i. e. during prepuberty. At this age there is a more rapid growth of the testes, penis and prostate, and an increased excretion of androgens. A subnormal excretion of androgens was demonstrated by Engberg (1948) in cryptorchid boys aged from 10 to 13; but the reduction was slight. It does not appear from his report whether these boys, apart from cryptorchidism, simultaneously exhibit clinically demonstrable pathological hypandry.

Retarded Development and Infantilism.

It is a well-known fact that retarded development may be universal in some cases and local in others, and to varying degrees (e. g. Horstmann, 1949) affects single functions such as, for example, sexual development, the growth of body length, the eruption of teeth, and mental development.

If a great number of functions are inhibited, it will be reasonable to use the term infantilism. If the growth of the body is sufficiently stunted, we speak of nanism. When the sexual development does not keep pace with the actual age, the case may, as suggested above, be labelled pathological hypandry.

In adult males i. e. men above the age at which puberty is normally concluded, the diagnosis of infantilism might possibly be supported by the presence of nanism as well as hypandry — to choose the two most apparent signs of retarded development.

If the concept of infantilism is to be maintained as a diagnosis applicable to child-patients, the demonstration of pathological hypandry cannot be a conditio sine qua non for upholding the diagnosis; but it would be reasonable to support this diagnosis on observation of the features that are known to be normally developing during childhood: height of body, maturing of epiphyses, stature, eruption of teeth, and psyche.

In the present work "infantilism" is defined as a state in which the somatic and mental development in several respects corresponds to an age lower than that of the patient in question. If the patient has passed the age of normal puberty, this diagnosis will also require the presence of pathological hypandry.

Retarded development will most clearly manifest itself by a low stature and retarded epiphyseal maturing. The concept of infantilism does not include the forms of nanism which are due to elective injury to the osseous system, as in rickets and chondrodystrophy. These patients will in many cases experience normal sexual maturation at the age when it is possible to decide with certainty whether they display a pathological hypandry. The term infantilism in childhood is reserved for the forms of retarded development which, from experience, are likely to be followed by retarded, slow or incomplete puberty — as was the case with the patients described by Lorain (1871), Brissaud (1907), and Levi (1908).

It may be pointed out that there is no general agreement as to the nosographic definition of infantilism. In his report of 1949, to which reference may be made, Horstmann gave a comprehensive survey of the different views of this problem, and suggested a delimitation of the concept of infantilism differing from the one maintained here, as he defined infantilism as "... a state in which a person in one or more respects, and at any rate as far as the genitals are concerned, presents a degree of development corresponding to an age earlier than his actual age."

With regard to adult patients Horstmann's and my definitions are in conformity, as we both establish pathological hypandry as a condition of infantilism. In the case of children, Horstmann draws the consequence of his definition and refrains from diagnosing infantilism. Since the affection which in adults reveals itself as infantilism has manifested itself already in childhood as retarded development in several respects, it must appear unsatisfactory not to diagnose the disease at this stage under its proper name, namely retardation of some function which, at the time in question, are normally being developed.

The present work distinguishes between primary and secondary infantilism. The term "secondary infantilism" is applied if there is supposed causal connection with a known affection, e. g. encephalitis, chronic enteritis, chronic nephritis, diabetes mellitus, bronchial asthma, and cranial or testicular traumata. Apart from traumatic infantilism, it will frequently be diffi-

cult to decide to what extent the pituitary gland and the testes are involved.

The other group is termed "primary infantilism" when it has been impossible to demonstrate any supposed causal affection.

In the literature on the subject this group is often referred to as "hypophyseal infantilism", but, with a few exceptions, it is not known with certainty whether the pituitary gland is the seat of the disease.

Pubertas tarda.

As is known, some children suffering from infantilism will, at the proper time, experience puberty with a normal course and development. According to my definition of infantilism, these patients must be regarded as recovered by the time of puberty, and their possible shortness of stature as adults is a defect following the infantilism during childhood.

Many patients suffering from infantilism will, at the proper time, present incomplete sexual development, which means that infantilism in these cases continues into adult age. As adults they are small and psychoinfantile, with pathological hypandry.

In the present series of cases there are, however, patients who have not, during childhood, presented symptoms of infantilism; they were of normal or almost normal height and proportions; and their genitals were of the same size as in other boys. Their only symptom is retarded or completely absent puberty. The morbid state of these patients will not be recognized until after the fifteenth year, when puberty has begun in the great majority of normal boys; in the present work they have been diagnosed "pubertas tarda (sensu strictiori)". This late or tardy puberty, which in patients suffering from infantilism is only a symptom of the general, retarded development, seems in such patients to be due to a more or less elective injury to the processes initiating puberty. The boys grow into (pathologically) hypandrogenic adults of a slightly subnormal height (the normal acceleration of growth during prepuberty fails to appear) or of normal, or above normal height (see eunuchoidism), and gradually they develop eunuchoid proportions.

Eunuchoidism.

The most important feature of the final prognosis is, of course, that puberty leads to complete sexual maturity.

A retarded and/or a too slowly developing puberty which is nevertheless completed may in man with fully developed virility leave a residual symptom in the form of eunuchoid proportions of the body.

In the present work the term "eunuchoid" is used to designate (pathologically) hypandroid adults with eunuchoid proportions. The group comprises patients with duly commenced, but incompleted puberty, besides inveterate cases of pubertas tarda, however, only patients who have not suffered from infantilism during childhood.

In the following survey of the series, the above-mentioned three groups (primary or secondary infantilism, pubertas tarda sensu strictiori, and eunuchoidism) are in some instances dealt with as one group termed "infantilism".

Adiposogenital Dystrophy.

Whilst the infantilism group is characterized by pathological hypandry in patients at or above the age of puberty, it is less certain that patients with adiposogenital dystrophy suffer from pathological hypandry. As the view of this affection has undergone certain changes in the course of time, in respect of nosologic delimitation as well as of etiology and prognosis, a survey of previous findings may be fitting.

This disease was first discovered by Pechkrantz (1899) in a boy, and by Babinski (1900) in a girl. Shortly after, in 1901, Fröhlich described a similar case in a boy. In 1908 Bartels suggested the term "adiposogenital dystrophy". The disease is characterized by fatness, especially localized to the breast, the lower part of the abdomen, the mons pubis, the hips, and the trochanteric region. In additions there are — actually or apparently — small testes and penis, and, occasionally, cryptorchidism. In many cases genu valgum may be observed. All patients reported by the three first-mentioned authors had a hypophyseal tumour. Sexual maturation was incomplete.

Some authors include dwarfs with feminine adiposity under

Fröhlich's syndrome (adiposogenital dystrophy). Such patients should, however, — as stressed by Horstmann — come under Brissaud's type, and be considered as having two affections: dwarfism and adiposogenital dystrophy.

The novel features of Pechkrantz's, Babinski's and Fröhlich's observations were not only the establishment of a subdivision of fat children, but also the demonstration of a hitherto overlooked connection between adiposity and the endocrine system.

Fröhlich maintained that the cause of the disease was the pituitary gland which had been injured by pressure. A few years later (1904) Erdheim ascertained the syndrome in a case of a tumour of the pituitary pedicle, whereas the gland proper was intact. Erdheim ascertained that a lesion of the basis cerebri rostrally to the pituitary gland was the sole cause of the syndrome.

Erdheim's view was supported by Smith (1927) who demonstrated that lesions of the hypophysis in rats cause adiposity only when the diencephalon is simultaneously affected. Genital atrophy could also be produced by hypothalamic lesions, but not so constantly and to such a degree as in hypophysectomy. Only occasionally a slight retardation of growth was observed. Rats are suitable animals for such experiments, since, in contrast with cats and dogs which had been used by previous authors, their basis cerebri is protected by a rigid diaphragm through which passes the pedicle. It is thus possible to produce lesions of the pituitary gland only.

The next step was to produce adiposity by injuring the hypothalamus without simultaneous lesion of the pituitary. This was managed by Hetherington and Ranson in 1939 by means of a Horsley-Clarke stereotaxic apparatus. In 1942 they demonstrated that adiposity may also be produced in hypophysectomized animals. Hypothalamic adiposity has later been produced in cats, dogs and monkeys. The essential feature of its genesis is a pronounced hyperphagia (Brobeck, Tepperman and Long, 1943; Brooks and Lambert, 1946). Besides adiposity, Hetherington and Ranson (1942) demonstrated decreased weight of the testes after the operation, but the relationship between the two phenomena is still obscure.

Thus, these experiments have corroborated Erdheim's

view of the hypothalamus as the etiological seat of adiposogenital dystrophy. But later investigations have made it equally clear that the syndrome of adiposogenital dystrophy is by no means specific to coarser anatomical lesions of the hypothalamus, since many writers (Shapiro, 1929; Ellis and Tallermann, 1934; Bornhardt, 1936; Dorff, 1936; Selander, 1937; Bruch, 1941) have reported series of cases of adiposogenital dystrophy without clinically demonstrable hypophyseal or hypothalamic lesions. It also appears that with regard to functions and development, such patients are in no way backward as compared to other adipose boys whose obesity is not of the typically feminine pattern. The prognosis of the state of adiposity after puberty is the same for both groups. In a follow-up of adipose youths aged 20 or more Mossberg (1948) found that those with comparatively slight obesity had, relatively, lost weight, whereas those with pronounced obesity had remained fat, apart from a transient loss of weight during puberty. The localization of the adiposity, on the other hand, had changed from the feminine to a more diffuse distribution. Nor did the metabolic rate or epiphyseal maturation differ from that of other fat boys.

The classic works on Fröhlich's syndrome (adiposogenital dystrophy) have demonstrated an enlargement of the opening of the pituitary fossa (Erdheim, 1904; Goldhamer and Schüller, 1925). Later Haas (1925) demonstrated a similar sellar figure in 1 out of 7 boys with adiposogenital dystrophy; 4 out of the remaining 6 had enlarged, and 2 normal, sellae. Reinert (1926—1927), among 10 boys with the same affection, found only 1 with a pathological — too small — sella. In 19 cases Mossberg found no sellae of classic shape; their volumes tended to be a little subnormal, but there was a considerably greater deviation than in normal persons. The slight diminution of the sella is not specific to this affection, as it was ascertained also in other groups of adipose patients (Mossberg).

The sexual maturation is of a special interest. The best indication of the degree of the genital dystrophy which is maintained to be present in these patients, is their ability to pass spontaneously through a normal sexual maturation. Shapiro (1929) found incomplete sexual maturity in only 2 out of 50

persons examined; Hering (1938) in 2 out of 11 (these two were, however, only 15 years old when examined); S. C. Werner (1941) in none out of 8; and Mossberg (1948) found no deficiency in the sexual maturity of his patients. According to Nobécourt's (1938) and Bruch's (1941) comprehensive surveys of the development of adipose boys, it seems, on the other hand, that their sexual maturing process sets in a little earlier than in normal boys; this in conformity with the fact that adipose boys also in other respects, with regard to height, epiphyseal maturing, and intelligence, are ahead of boys of the same age, which was also found by Mossberg. However, Shapiro (1929), who examined 48 boys with adiposogenital dystrophy, found that in the higher forms at school they were some years older than their classmates, possibly on account of transient stagnation of mental development. His report mentions no control series of other adipose boys.

It must, however, be pointed out that, unlike Mossberg and others, Bruch does not distinguish between different types of adiposity. On the other hand, the photographs reproduced in her report show patients with typical adiposogenital dystrophy, and her conclusions must therefore be supposed in all essentials to apply also to this type of adiposity.

The therapeutical results do not support the theory that adiposogenital dystrophy is of endocrine origin. Thus, Dorff (1936), Gordon (1937), Plum (1937), Sand and Plum (1938), and Chiari (1938) have not been able to demonstrate any effect of treatment with hormone (chorionic gonadotropin) on the adiposity of these patients.

The conclusion of these examinations is that, with regard to the degree of adiposity and the processes of puberty, patients suffering from adiposogenital dystrophy do not differ from the great majority of adipose boys, but that the special localization of the obesity may be taken as a feature of the sexually immature period; in other words, that the infantile habitus is a pathoplastic factor that may influence the distribution of adiposity. Adiposogenital dystrophy, in the sense which this term has gradually acquired, has thus been restricted to an anthropometric variation among adipose boys, and there appears to be no justification for the sharp distinction between this state and that of "common" infantile adiposity, especially

since the supposed hypogenitalism has proved to be an illusion founded on the fact that the genitals are partly buried in fat. As already mentioned, Bruch did not place these patients in a special group in her series of cases, and Heller and Nelson (1948) state that "... adiposogenital dystrophy and other such anthropometric designations are meaningless anachronisms of a previous era".

There now remains Fröhlich's and Erdheim's original syndrome, a term that should rightly be applied only in cases of adipose boys and men with pathological hypandry and signs of affection of the mesencephalon.

Sexually mature Dwarfs.

This term has been suggested by Horstmann (1949) to cover a type of patients who, as children, are smaller than others of the same age, in whom puberty sets in early and quickly, the epiphyseal lines are closed more rapidly than the normal, and the accelerated growth of body height, normally observed during prepuberty and puberty, sets in at an earlier stage and is of shorter duration. The extremities are short as compared with the trunk, whereas the reverse is the case in eunuchoidism. The renal androgen excretion during puberty is within normal limits and the patients cannot, therefore, be described as hyperandrogenic.

The seat of these disturbances of growth and sexual maturation is unknown.

Testicular Hypoplasia.

This group comprises patients above 20 years of age without, or with only slight, hypandry, and with a volume of the testes below 10 ml.

Chapter XV

WRITER'S EXAMINATIONS OF THE CORRELATION BETWEEN THE CONCENTRATION OF PHOSPHATASE AND THE OTHER SOMATIC SEX CHARACTERS IN HYPANDRY AND CERTAIN OTHER CONDITIONS

The purpose of the present examinations is to determine the production of phosphatase in hypandrogenic conditions, determined by the concentration of phosphatase in the expressed secretion and to determine its applicability as an indicator of the androgen production of the organism.

Composition of the Series:—

The series consists of 166 men under 60 years, and may be divided into the following groups:—

A. Seventy hypandrogenic boys or men, not previously treated with sex hormones (including the 13 normal boys in Table XI a). See Table XVI.

B. Fifty-one hypandrogenic boys or men, previously treated with sex hormones. See Table XVII.

C. Twenty-two hypandrogenic imbeciles, aged 12 to 17, not previously treated with hormones. See Table XVIII.

D. Twenty-two men with impotentia coeundi, without hypandry. See Table XXIII.

(E.) Four boys or men with gynaecomastia. Three of them (Nos. 47, 127, and 187) are also listed under group A (Table XVI), and the two latter of these (Nos. 127 and 187) are, besides, tabled as „Normal during Puberty" (Table XI a).

Comments on Groups A and B. Hypandrogenic Boys or Men.

These two groups have been arranged so as to comprise vary-

ing degrees and kinds of physiological or pathological hypandry, with or without nanism, with or without adiposity, and the individuals examined are of different ages. If the concentration of phosphatase in such a heterogeneous series shows correlation to the degree of development of the sex characters, it must constitute a rather specific function of the androgen production.

The various conditions are represented in the two groups as follows:—

	Group A. Table XVI	Group B. Table XVII
Primary Infantilism	17	7
Secondary Infantilism	6	5*)
Retarded Puberty	4	2
Eunuchoidism	2	16
Adiposogenital Dystrophy	12	18
Normal Persons under 20 (see also Table XI a)	13	
Testicular Hypoplasia (see also Table XXII)	11	2
Sexually mature Dwarfs	3	
Pubertas praecox adrenalis	1	
Evolutio praecox	1	
Cryptorchismus anteus		1
Total	70	51

In Groups A and B — as well as in the following ones — each individual is characterized by the phosphatase concentration ascertained in the expressed secretion first obtained, but the concentration of secretion number two is also given in the tables for comparison.

In three cases only this principle was abandoned. In these (Nos. 106, 113, and 163) the phosphatase concentration in the first expressed secretion was found to be subnormal; in the second secretion it was normal without intervening hormone treatment. These three cases are listed in Tables XVI and XVII under the second, normal, concentrations. According to Table XIV, showing the various details, the difference in No. 106 may be partly explained by varying admixture to the prostatic secretion. With regard to No. 113, the production of testicular hormones may possibly have increased spontaneously during the five months between the first and second expressions.

*) Two of these patients (Nos. 36 and 42; se Case Records) are suspected of having the "Fröhlich-Erdheim" syndrome. The presence of a hypothalamic affection is, however, not certain. —

Table XIV

Three Subjects who showed a Subnormal Concentration of Phosphatase in the first expressed Secretion but later had a normal Concentration.

No.	Date	Concentration of phosphatase stated in K.P.U.	Amount of expressed secretion in mm³	Appearance of expressed secretion (see page 74)	*Admixture of urine* mm³ secretion	mm³ urine	mm³ in per cent	*Admixture of vesicular secretion* mm³ secretion	gammas of fructose
106	5.7.46	4.7	120	4	50	0	0		
	7.7.46	2.7	170	4	50	6	12		
	25.7.46	1.4	90				+		
	24.4.47	6.4	110	4	50	ca. 5	ca. 10	40	1
113	23.7.46	1.5	5	2					
	12.12.46	5.5	33		13	0	0		
163	5.3.47	3.0	95	4	50	0	0	25	1
	13.3.47	7.2	110	4	50	0	0	40	0
	20.3.47	8.6	170	4	50	0	0	50	7

Classification by Intensity of Production of Phosphatase.

The following classification will be used in the following: no secretion to be expressed, secretion to be expressed with subnormal and normal phosphatase concentration, respectively.

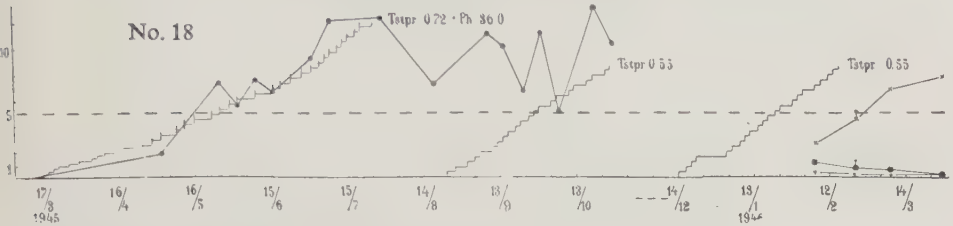
No Expressed Secretion. In 23 persons in all it was impossible to express secretion (Nos. 18, 36, 49, 55, 68, 69, 70, 79, 97, 119, 123, 126, 149, 151, 170, 172, 174, 190, 191, 192, 193, 194, and 196). After the attempt at expression they were all treated with chorionic gonadotropin or testosterone, which rendered possible the expression of secretion in all cases. In 20 out of the 23 persons, the very first or one of the first secretions expressed during treatment contained phosphatase concentrations of < 1 K. P. U. In the remaining three (Nos. 18, 68, and 69) the concentrations were between 1 and < 5 K. P. U. Subsequent experiences with No. 18 (see Fig. 15) show that the power of ejaculation ceases when treatment is discontinued. In Nos. 68 and 69, repeated experiments proved that it was impossible to express secretion before and during beginning of the treatment, whereas it was easily possible towards the end of treatment and later (see Fig. 24).

It is then reasonable to suppose that in all 23 cases — at the time when it was impossible to express secretion — the prostate either did not produce any secretion or produced but scanty

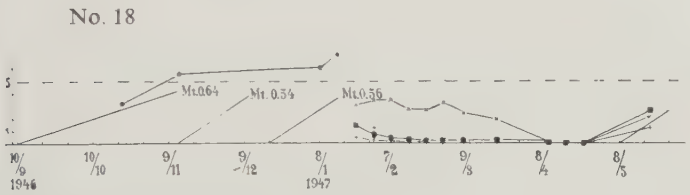
Figure 15.

The Concentration of Phosphatase in the Course of Treatment with Chorionic Gonadotropin and Testosterone, respectively Treatment with Chorionic Gonadotropin, of 2 Eunuchoids (see pages 142 and 144).

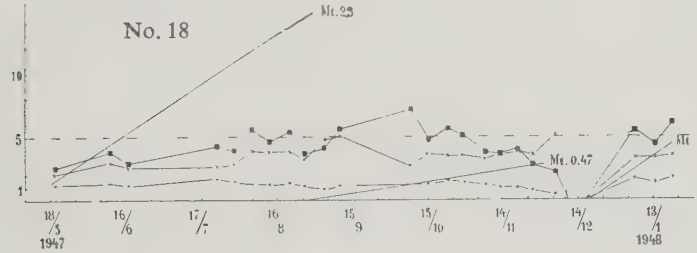
Ordinate: Concentration of phosphatase in K.P.U.
See also explanation in text, page 81.



Single dose of testosterone propionate 10, 25, 25, 25 mg
Single dose of Physex 1500 I.U.

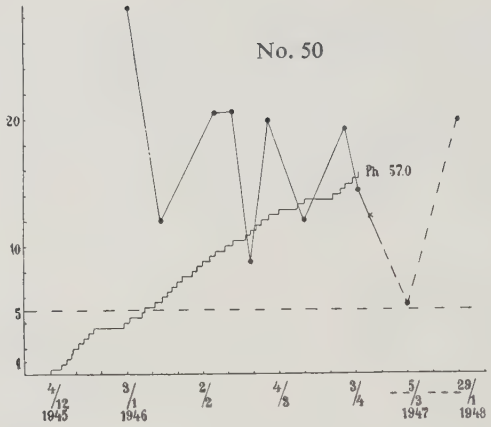


■ - ■ amount of phosphatase per ejaculate
×—× concentration of phosphatase in ejacnlate
+—+ volume of ejaculate in ml
Daily dose of methyl testosterone 10, 20, 20, 20 mg



Daily dose of methyl testosterone 20, 5, 20 mg

After discontinuation of each treatment with testosterone the power of ejaculation ceases, and it becomes impossible to express prostatic secretion.



Single dose of Physex 1500 I.U.

On March 5th, 1947, diabetes mellitus c acidose was ascertained.

On Jan. 29th, 1948, the diabetes was well-compensated.

The production of phosphatase continued in spite of discontinuance of treatment.

quantities containing no phosphatase. In Tables XVI and XVII this state is termed phosphatase concentration "0".

One person has been left out from this series (No. 50, see Fig. 15), as it cannot be stated with a sufficient amount of certainty that production of phosphatase did not take place despite failing expression of secretion, because, 21 months after the cessation of the ensuing treament, expressed secretion with normal phosphatase concentration was obtained; somatic and functional state was then — in contrast with Nos. 68 and 69 — exactly as before the first examination.

Phosphatase Concentrations < 5 K. P. U.

Such a subnormal concentration was found in a total of 29 persons. It is evident that a decreased phosphatase concentration in the expressed secretion does not, as a matter of course, always mean a decreased secretion of phosphatase in the prostatic secretion, as an admixture of other fluids during expression may reduce the phosphatase concentration. Additional tests to prove or to show the probability that the production of phosphatase, as defined in the present work, are actually reduced, are as follow: —

Repeated expressions, as several though scanty quantities of expressed secretions without or with only low phosphatase con-

centrations, increase the probability that the production is reduced.

creatinine tests, preferably repeated with sufficient quantities of expressed secretion ($\geqq$ 10 mm^3);

fructose analyses, provided there is a visible admixture to the expressed secretion of non-serous matter; and, finally, if expressed secretion is obtained in exceedingly small quantities:—

treatment with chorionic gonadotropin or testosterone, during which repeated expressions are performed. In most cases the quantities of expressed secretion will increase during treatment, supplying sufficient material for creatinine and fructose analyses; the phosphatase concentration will also gradually increase.

In the above-mentioned individuals it was made sure by one or more of the methods mentioned, that the expressed secretion was identical or almost identical with the prostatic secretion. In 14 cases, 10 mm^3 or more of the first and/or second expressed secretions were therefore examined for admixture of urine: 10 cases contained no urine; in the other cases the findings were: 2 and 0 per cent. (No. 108); 6 and 7 per cent. (No. 136); 3 and 0 per cent. (No. 187); and 10 and 12 per cent. (No. 501). In 16 instances, expressed secretions obtained at a later stage were repeatedly examined for urine. Only in one (No. 7) urine was demonstrated, varying between 20 and 60 per cent., once even reaching 90 per cent.

Thirteen persons with subnormal phosphatase concentration in the expressed secretion have not been considered in this series, as it proved impossible to avoid dilution of the prostate secretion during expression. These 13 cases are listed in Table XV. In subsequent expressed secretions obtained from No. 1, considerable admixtures of urine were found (the first secretions were not examined for urine). That expressed in No. 11 was postejaculatory (see p. 103). In the 11 last cases, expressed secretion was obtained once only and in such small quantities that examinations for admixtures proved impossible.

Phosphatase Concentrations $\geqq$ 5 K. P. U. were ascertained in a total of 69 persons. Possible admixture of other secretions during expression may have influenced their respective placing within the normal range.

Comments on Group C. Imbeciles during Puberty.

In each of these patients only one expression or attempted ex-

Table XV

Thirteen Individuals with decreased Concentration of Phosphatase in the expressed Secretion in whom an essential Dilution of the Prostatic Secretion cannot be excluded. Arranged according to increasing Concentration of Phosphatase.

No.	Concentration of phosphatase stated in K.P.U.	Amount of expressed secretion in mm	Volume of testes in ml	Diameter of penis in mm	Length of penis in mm	Pubes	Terminal growth of hair
103	"0"	2	2.3	18	55	1	0
	0.5						
155	"0"						
	0.9	16	9.6	22	82	2	1
94	0.1	7	7.1	14	37	0	0
138	0.1	8	1.6+s	20	46	4	2
96	0.2	10	2.4	16	33	1	0
186	0.2	13	16.4	26	62	3	2
304	0.3	10	12.2	21	54	3	1
312	0.6	15	9.7	19	54	2	1
153	0.7	1	5.5	23	66	5	3
303	0.9	17	13.4	20	55	2	0
145	1.2	1	4.8	19	58	2	2
1	2.5		d +1			4	3
	2.0						
11	3.6		c. 6			6	4

*) : previously treated with hormones.

pression was made. The series also concludes patients from whom it was impossible to express any prostatic secretion. They are marked "0", in spite of the fact that the therapeutical test already mentioned has not been made. Patients with small quantities of expressed secretion with a subnormal phosphatase concentration have also been included in spite of the fact that only one expression was made.

Comments on Group D. Impotentia coeundi.

This group comprises patients suffering from functional impotence without somatic hypandry.

Two patients have been left out of this series, one on account of simple recurrent postgonorrhoeal urethritis; the other because all expressed secretions contained considerable admixtures of vesicular secretion.

Further, the principle of characterizing the patients according to the phosphatase concentration of the expressed secretion first obtained, has been abandoned in two cases (Nos. 110 and 159) for whom results of the second expression are given. In both instances, the first expressed secretion contained subnormal, the second normal, phosphatase cencentrations. In neither of the patients the admixture of urine can be excluded as a possible cause of the lower concentration in the first expressed secretion.

Prostate	Appearance of expressed secretion	Androgenuria in I U. (biometrical)	Height	Height when sitting	Age	Diagnosis
0			147		16.1	Infantilismus primarius*)
	2					
					16.3	Infantilismus primarius
2	1		145	71	17.0	
0	1		145	70	14.9	Infantilismus primarius
1	2				15.5	Adipositas m.g. Infantilismus
0	1		145	67	13.4	Normal
2	1				13.3	Dystr.adip.-gen.*)
					15	Infantilismus primarius*)
					14.10	Infantilismus*)
0	1	5			34.2	Eunuchoidismus Ejaculate no phosphatase
					17.6	Infantilismus primarius
1			146	72	15.6	Infantilismus primarius*)
2	1		167	81	20.2	Eunuchoidismus*)
4		45	180		33.7	Hypoplasia testis

Results ascertained with Regard to the Correlation between Phosphatase Concentration and other Somatic Sex characters.

Group A. Hypandrogenic Boys and Men, not previously treated with Sex Hormones.

In Table XVI the patients are listed according to the size of phosphatase concentrations. It can be seen directly that there is a connection between the size of the phosphatase concentration and the degree of hypandry, as previously demonstrated in a smaller series by the writer (1945). The correlation between phosphatase concentration and development of the different sex characters appears from Table XIX which also shows the correlation in some of the subdivisions of patients not previously treated. This correlation will be discussed in the following.

Table XVI

The Concentration of Phosphatase and other Properties in 70 previously untreated Individuals, arranged according to rising Concentration of Phosphatase.

No.	Concentration of phosphatase in first expressed secretion stated in K.P.U.	Concentration of phosphatase in second expressed secretion stated in K.P.U.	Volume of testes in ml	Diameter of penis in mm	Length of penis in mm	Pubes	Terminal growth of hair	Prostate
49	"0"	"0"	c. 2			0	0	0
68	"0"	"0"				0	0	1
70	"0"	"0"	<1			0	0	0
79	"0"	"0"	<1	<15	<20	0	0	0
97	"0"	"0"	2.6	15	21	0	0	
119	"0"	"0"	d+ 3.3	15	20	0	0	0
123	"0"	"0"		<15	<20	2	1	0
126	"0"	"0"	d+s <1	<15	<20	0	0	0
149	"0"	"0"	2.7	15	35	0	0	1
170	"0"	"0"	2.0	13	37	0	0	1
172	"0"	"0"	15.0	22	55	1	0	0
174	"0"	"0"	d + <1	<15	<20	0	0	0
190	"0"	"0"	2.3	16	37	0	0	1
191	"0"	"0"	6.4	17	48	1	1	0
192	"0"	"0"	6.6	20	51	1	0	0
193	"0"	"0"	1.0	14	24	0	0	0
194	"0"	"0"	c. 1	14	27	0	0	0
196	"0"	"0"				0	0	0
35	<0.1	<0.1	c. 3	16	20	2	2	1
54	<0.1	<0.1	2.9	17	43	1	0	1
80	<0.1	0.1				2	1	
108	<0.1	0.4	16.4	22	84	2	1	
136	0.1	<0.1	4.4	16	35	2	1	1
150	0.1	<0.1	12.4	23	60	2	1	1
98	0.3	0.2	3.3	19	36	2	2	2
134	0.4	0.7	2.6	19	50	3	1	2
199	0.4		5.2	27	49	2	1	1
66	0.5	0.8	c.1.5	20	33	2	1	
166	0.6	0.6	21.1	27	94	6	3	4
187	1.2	1.4	18.5	25	76	2	1	4
501	1.8	2.8	22.6	27	72	3	2	2
164	1.9	1.9	14.5	30	89	3	3	1
74	2.2	1.3	11.9	24	68	2	1	
141	2.4	1.5	8.5	28	75	3	3	4
63	3.5		<1.5			0	0	
502	3.6		28.1	25	75	6	3	4
305	4.5		16.3	26	69	6		
503	5.1		18.9	27	90	3	1	1
106	6.4		8.2	27	86	6	4	2
112	6.6		17.8	29	100	6	4	4
127	6.6	9.6	9.9	34	88	5	2	
157	7.0	10.7	14.0	24	75	2	1	1
179	7.4		6.5	25	71	6	4	
115	8.3	9.4	10.8	30	80	3	1	
162	8.9		18.0	28	104	4	2	
76	9.3	6.6	5.0	24	75	6	4	

Appearance of expressed secretion	Androgen-uria in I.U.	Height	Height when sitting	Age	Carpal bone age	Diagnosis
	2	144	70	16.9	11.3	Infantilismus primarius
		154	75	12.9		Dystrofia adiposo-genitalis
		148	72	13.8		Dystrofia adiposo-genitalis
	<1	129	62	19.5	12.3	Infantilismus secundarius
		159	76	14.1	12.9	Infantilismus primarius
		150	74	12.1	12.9	Dystrofia adiposo-genitalis
		138	67	15.9	15.9	Infantilismus primarius
		114	54	18.11	11.0	Infantilismus secundarius
		168	77	17.5		Pubertas tarda
	2	158	77	15.1	11.0	Infantilismus primarius
	3	151	72	17.4	12.9	Pubertas tarda
	2	142	70	12.4	10.9	Dystrofia adiposo-genitalis
		141	67	15.3		Infantilismus primarius
		155	72	16.2		Pubertas tarda
		148	68	15.3		Infantilismus secundarius
				11.11		Dystrofia adiposo-genitalis
		143	68	18.7		Infantilismus primarius
		137	68	13.6	12.3	Infantilismus primarius
1	8	165	78	16.6		Dystrofia adiposo-genitalis
1		149	71	16.0	13.3	Infantilismus primarius
1		138	64	14.8	11.9	Infantilismus primarius
1	15	144	72	15.5		Infantilismus secundarius
1		151	61	13.11	14.3	Dystrofia adiposo-genitalis
1		163	79	13.7		Normal
1				14.3	14.0	Dystrofia adiposo-genitalis
2		164		13.9	13.9	Dystrofia adiposo-genitalis
2		149	72	16.2	13.3	Infantilismus primarius
1	7	155	74	16.0	12.9	Dystrofia adiposo-genitalis
1		154	79	18.6	16.0	Infantilismus primarius
2		167	79	14.1		Gynæcomastia in normal pub.
2		160	77	16.5		Normal
3	1	158	76	19.1		Pubertas tarda
2	9	144	71	17.4	12.0	Infantilismus secundarius
2	5			16.4	11.6	Infantilismus primarius
4		152	70	12.8	11.9	Dystrofia adiposo-genitalis
4		165	83	16.9		Normal
				20.7		Infantilismus primarius
3		161	79	14.7		Normal
4	40	173	84	50.4		Hypoplasia testis
4		187	90	32.5		Hypoplasia testis
4	11			13.6	13.3	Gynæcomastia in normal pub.
3	5			15		Normal
4		168	84	59.10		Hypoplasia testis
4		149	73	16.5	14.3	Infantilismus primarius
4		164	82	18.8	17.9	Infantilismus secundarius
	45	168	82	38.11		Hypoplasia testis

Table XVI (cont.

No.	Concentration of phosphatase in first expressed secretion stated in K.P.U.	Concentration of phosphatase in second expressed secretion stated in K.P.U.	Volume of testes in ml	Diameter of penis in mm	Length of penis in mm	Pubes	Terminal growth of hair	Prostate
143	9.7	10.7	15.3	24	100	6	3	4
64	9.8	8.1	19.6	21	65	2	2	2
65	9.8					6	4	
250	10.2	5.3	1.1	29	83	3	2	2
139	10.8	11.9	c. 1		75	2	1	2
507	10.9		17.1	28	72	4	2	2
78	11.0	11.0	6.2	23	87	6	4	4
135	11.0	16.6	9.8	24	71	3	3	4
72	11.1	10.6	35.0	24	73	6	4	
144	12.3	10.9	1.5	26	96	6	4	4
47	13.1	9.0	7.8	23	50	6	4	4
173	13.2		31.3	25	65	5	2	4
504	13.4	6.2	15.2					
45	13.9	7.6	c. 7			6	4	4
505	13.9		28.2	28	95	3	3	4
142	14.3	16.3	3.7	27	67	6	4	4
122	15.1		14.3	25	59	6	2	4
51	15.2	12.6	16.9	22	70	6	2	4
9	15.7	16.3	c. 7			6	4	4
188	16.2	17.0	29.8	31	109	6	3	4
53	18.5		2.6	23	82	6	4	4
169	18.7		20.8	28	95	3	1	4
506	19.9		24.1					
156	23.5		20.2	34	110	4	1	2

In column 4, d (respectively s) means retention of the right respectively left, testis. With regard to the measuring of the testes and penis, see page 49. The degrees stated in columns to 10 refer to the statements on page 53.

Table XVII

The Concentration of Phosphatase and other Properties in 51 previously treated Individuals, arranged according to rising Concentration of Phosphatase.

18	"0"	"0"	c. 1	22	45	2	1	0
36	"0"	"0"	c. 2.5	19	50	2	1	1
55	"0"		c. 5			2	1	1
69	"0"	"0"	c. 1		60	2	2	0
151	"0"	"0"	0.8+s=1-2	<15	<20	2	1	0
42	<0.1	0.1	1.6	15	42	2	1	1
133	<0.1	< 0.1	1.5	16	36	2	1	1
251	<0.1		d+s	19	40		1	1
128	0.1		d+s	18	22	0	0	1
7	0.6	0.4	c. 1	13	19	2	2	1
8	0.6	1.1	5.4	20	35	3	1	2

Appearance of expressed secretion	Androgen-uria in I.U.	Heigbt	Height when sitting	Age	Carpal bone age	Diagnosis
4		165	85	18.8	> 18.9	Normal
3	13	177	84	29.10	16.9	Eunuchoidismus
	25	140	72	18.0	> 18.9	Sexually mature dwarf
4		184	85	27.7		Eunuchoidismus
3	20	108		3.2	9.0	Pubertas præcox adrenalis
3		161	75	16.8		Normal
4	35	168	83	40.9		Hypoplasia testis
4		157		16.6		Sexually mature dwarf
4	11	156	82	18.0	18.3	Sexually mature dwarf
3	7	161	80	35.0	18.9	Hypoplasia testis
3	6			49.6		Hypoplasia testis
4		180	88	14.6		Dystrofia adiposo-genitalis (sanata)
4	23	166	83	19.11		Normal
4	23	159		23.9		Hypoplasia testis
4		161	80	16.0		Normal
4	25	171	83	30.4	> 18.9	Hypoplasia testis
4	14	174		13.6	14.3	Evolutio præcox
3	13	152	76	18.0	16.6	Infantilismus primarius
4				29.11		Hypoplasia testis
4		159	81	19.5	18.9	Infantilismus primarius
4	62	173	81	24.9		Hypoplasia testis
4		167		17.1		Normal
		159	79	16.9		Normal
4				17.6	14.9	Infantilismus primarius

	50			19.8		Eunuchoidismus
	1	147	72	21.5		Infantilismus secundarius
	<1	150	72	16.8	13.3	Infantilismus secundarius
	5	182	83	24.7	14.0	Eunuchoidismus
	1	152		14.1		Dystrofia adiposo-genitalis
1		162	75	20.11	15.0	Infantilismus secundarius
1		162		13.9		Dystrofia adiposo-genitalis Hypometabolismus
1		161	79	18.3		Eunuchoidismus
1		155		13.4		Infantilismus secundarius
1	13			32.10		Eunuchoidismus
1		150		16.10		Infantilismus primarius

Table XVII (cont

No.	Concentration of phosphatase in first expressed secretion stated in K P.U.	Concentration of phosphatase in second expressed secretion stated in K.P.U.	Volume of testes in ml.	Diameter of penis in mm	Length of penis in mm	Pubes	Terminal growth of hair	Prostate
160	1.5		15.0	24	90	5	2	2
59	1.9	1.2	17.0	24	77	6	2	
309	2.1	5.5	17.6	33	84	6	4	2
165	2.4	0.1	5.9	20	35	4	3	2
100	5.3		23.8	26	51	6	4	3
113	5.5		23.8	27	89	6	3	
10	5.6	0.7	c. 1.5	32	110	6	2	4
168	5.6	7.8	d+s			6	2	2
311	6.4		14.8	27	46	3	3	4
5	6.8	9.3	13.5	28	64	6	3	
310	7.2		17.8	20	33	6	2	
316	7.2	3.4	5.7	23	79	6	4	
16	7.7	9.6	c. 20	25	80	6	3	2
41	8.0	5.9	3.3	16	50	3	1	2
154	8.0	8.2	9.6	20	67	2	1	2
189	8.5	7.1	9.8	28	71	4	1	4
163	8.6	-	18.5	30	61	4	2	2
28	9.3	9.3	c. 26	25	55	3	3	2
46	9.6	9.9	24.6	23	87	6	4	4
171	10.2		19.9	32	90	6	4	4
33	10.5	3.5	c. 5	20	60	6	4	2
302	12.4		32.4	26	52	6	4	4
3	12.6	12.0	c. 50	35	100	6	2	2
32	13.1	12.5	c. 18			6	4	3
176	13.3		10.4	30	104	6	4	4
52	13.7	15.8	11.5	24	42	4	2	4
21	14.2		c. 25			6	4	4
121	14.3	4.1	11.1	29	50	6	4	
61	14.8		16.1	24	82	6	3	
67	14.9		15.3	23	75	6	4	4
4	16.3	17.3	c. 15			6	4	
12	16.7	17.1	3.4	25	53	4	3	2
315	17.3	12.6	12.7	26	80	5	1	
20	17.8		c. 25			6	4	4
167	18.1		18.8	24	80	5	2	4
195	18.5		0.8	29	77	4	3	2
308	19.5	4.6	28.9	30	80	6	4	

Appearance of expressed secretion	Androgen-uria in I.U.	Height	Height when sitting	Age	Carpal bone age	Diagnosis
3		157		16.1	14.3	Infantilismus primarius
4		171	83	14.6		Dystrofia adiposo-genitalis in sanatione
3				26		Pubertas tarda (sanata)
2	5			36.5		Eunuchoidismus
4		167	83	21.0	> 18.9	Dystrofia adiposo-genitalis (sanata)
3		178	83	15.0		Dystrofia adiposo-genitalis (sanata)
3		178	83	21.9		Eunuchoidismus
3		183	86	17.5		Eunuchoidismus
3				28.4		Eunuchoidismus
				31.10		Eunuchoidismus
3				17.8		Dystrofia adiposo-genitalis (sanata)
3	30			31		Hypoplasia testis
4				20.9		Eunuchoidismus
		150		15.4		Infantilismus primarius
3		153	76	17.5	14.0	Infantilismus primarius
3		155	76	20.9		Infantilismus primarius
4		171	84	15.2	15.6	Dystrofia adiposo-genitalis (sanata)
	25			24.8		Eunuchoidismus
3		177		19.1		Dystrofia adiposo-genitalis (sanata)
4		166	85	21.1		Infantilismus primarius (sanata)
4				59.0		Hypoplasia testis
4				37		Dystrofia adiposo-genitalis (sanata)
4				20.11		Eunuchoidismus
				22.4		Cryptorchismus antea
4		180	86	20.11		Dystrofia adiposo-genitalis (sanata)
4	2			12.8		Dystrofia adiposo-genitalis
				19.9		Dystrofia adiposo-genitalis (sanata)
4	15			20.7	> 18.9	Dystrofia adiposo-genitalis (sanata)
4	19			19.6	15.9	Infantilismus secundarius
4				24.10		Dystrofia adiposo-genitalis (sanata)
4				24.6		Dystrofia adiposo-genitalis (sanata)
4				31.5		Eunuchoidismus
4				14.3		Dystrofia adiposo-genitalis
4				21.1		Dystrofia adiposo-genitalis (sanata)
4		172	85	19.0	17.3	Infantilismus primarius
4		176	85	18.10		Eunuchoidismus
4	45			35		Eunuchoidismus (sanata)

Table XVII (cont

No.	Concentration of phosphatase in first expressed secretion stated in K.P.U.	Concentration of phosphatase in second expressed secretion stated in K.P.U.	Volume of testes in ml.	Diameter of penis in mm	Length of penis in mm	Pubes	Terminal growth of hair	Prostate
19	20.0		c. 25			6	4	4
306	21.8		23.4	27	75	6	4	4
314	24.2		12.3	26	96	6	4	4

For explanation see Table XVI.

Table XVIII

Concentration of Phosphatase and other Properties in 22 Pubescent Imbeciles arranged according to rising Concentration of Phosphatase.

No.	Concentration of phosphatase in expressed secretion stated in K.P.U.	Volume of testes in ml.	Diameter of penis in mm	Lenght of penis in mm	Pube
402	"0"	5.3	17	43	0
404	"0"	5.7	20	35	1
406	"0"	3.6	19	38	0
407	"0"	5.2	22	59	0
408	"0"	4.8	17	42	1
415	"0"	17.0	26	80	2
420	"0"	13.0	23	61	0
409	< 0.1	1.6	18	53	0
419	< 0.1	11.3	27	74	3
417	0.2	5.9	25	70	2
412	0.6	9.7	26	68	2
405	0.8	17.8	23	57	2
411	1.4	7.1	26	78	2
422	1.6	12.0	34	101	3
418	2.2	17.4	25	80	3
410	3.3	21.0	26	74	2
421	5.0	6.4	27	73	2
413	5.7	12.2	25	76	5
401	13.8	13.5	26	76	4
416	14.0	14.4	32	75	6
403	14.C	11.6	31	99	4
414	15.7	d+s	31	59	3

For explanation, see Table XVI.

Table XIX

The Individuals of the Various Groups, distributed according to Concentration of Phosphatase and the other Sex Characters (see also Tables XVI, XVII and XVIII).

ppearance expressed secretion	Androgen-uria in I.U.	Height	Height when sitting	Age	Carpal bone age	Diagnosis
4				21.11		Dystrofia adiposo-genitalis (sanata)
4				25		Pubertas tarda (sanata)
4		194	94	24		Eunuchoidismus (sanata)

Termi-nal growth of hair	Prostate	Appearance of expressed secretion	Height	Age
0	0		151	14.10
0	0		151	14.9
0	1		149	14.0
0	1		153	14.5
0	1		143	14.2
1	1		157	14.6
0	0		159	13.7
0	1	1	158	14.3
2	2	2	149	13.10
2	1	3	154	13.9
1	2	2	160	17.9
1	1	1	160	14.11
2	2	3	164	15.4
1	2	2	164	14.3
1	1	3	159	12.11
1	1	2	163	16.0
1	2	3	160	13.4
2	4	4	160	15.0
1	2	4	168	16.6
2	2	4	167	13.10
1	2	4	175	16.3
2	2	3	151	14.9

See at the end of the book.

Volume of Testes and Production of Phosphatase.

The correlation between these two sex characters is insignificant. There are two remarkable features: (1) The phosphatase concentration may be normal even when the testes are very small, as in patients 139, 144, and 250. The first was a boy aged 3, suffering from hyperplasia adrenalis and pubertas praecox, and his normal phosphatase concentration (i. e. normal for an adult) may well have been maintained by the androgen production of the suprarenal glands. (2) Subnormal phosphatase concentrations are more frequently accompanied by a normal volume of the testes than by normal development of the other accessory sex characters examined. Eight out of the 10 patients with a normal volume of the testes, but with a subnormal phosphatase concentration, are -- judged by the pubic hair — in the initial stage of puberty. A volume of the testes above 10 ml will, therefore, frequently develop at an earlier stage of puberty than a normal phosphatase production does.

Size of Penis and Production of Phosphatase.

The diameter and length of the penis grow with increasing phosphatase concentration. A person with a diameter of the penis below 20 mm or a length of the penis below 50 mm has little or no production of phosphatase. A diameter of the penis $\geqq 25$ mm and a length of the penis $\geqq 60$ mm will, in most cases, mean a production of phosphatase of a certain magnitude.

Pubic Hair and Production of Phosphatase.

The growth of pubes is one of the first and most significant signs of the onset of puberty. It appears from the table that the prostate does not produce any secretion during prepuberty, but about the time of appearance of the first pubic hairs it will generally begin producing a secretion of a low phosphatase concentration which gradually rises to normal, while the pubes grow denser and more widespread.

Terminal Hair and Production of Phosphatase.

The table shows that phosphatase production begins before the appearance of hirci, but that it does not reach normal concentration until the growth of beard has become vigorous.

Size of Prostate and Production of Phosphatase.

The table shows that the production of phosphatase begins before the gland is fully developed; the production is rarely normal before the prostate can be distinctly palpated as a prominence.

Appearance of Prostatic Secretion and Production of Phosphatase.

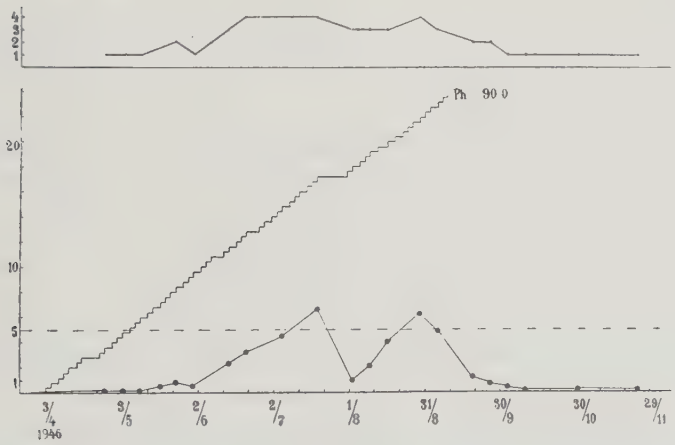
Normal prostatic secretion appears as a serous, homogeneous, milky fluid; the milky appearance is due to lipoid substances, which according to H u g g i n s (1945) are produced by genuine secretion.

As appears from the table, the appearance of the secretion is clearly correlated with the phosphatase concentration. Secretion without any phosphatase is as clear as water, but, with increasing content of phosphatase, it passes through all phases, from a

Figure 16.

Simultaneous Variations of the Concentration of Phosphatase
(lower curve, ordinate: concentration of phosphatase in K.P.U.
and of Appearance of expressed Secretion
(upper curve, ordinate: 1, watery, 2, opaque, 3, like skimmed milk, 4, milky)
in the Course of Treatment with Chorionic Gonadotropin.

Single dose of Physex 1500 I.U.
See also explanation on page 81,
No 79



The appearance of the expressed secretion follows its concentration of phosphatase

cloudy appearance to that of skimmed milk and to that of faintly transparent milk. These changes are particularly characteristic and rapidly appearing with the increasing production of phosphatase during gonadotropin or testosterone treatment of severe cases of hypandry, see Fig. 16. From this it may be concluded that the lipoid secretion of the prostate is also an accessory sex character, and since the change in appearance and the increase of the phosphatase concentration also in the course of such provoked accelerated sexual maturation are parallel, it may be concluded that the lipoid secretion is sensitive to much about the same extent as the phosphatase production to the androgenic hormones; this is presumably due to the production of testicular hormones enabling the secretory apparatus in the glandular epithelium of the prostate to function, thereby probably supporting all the attendant functions, such as the production of phosphatase, lipoids, citrate and protein.

Excretion of Androgens in Urine and Production of Phosphatase.

The table shows the striking facts that the phosphatase concentration may become normal while the androgen excretion remains quite low, and that the combination normal androgenuria: subnormal production of phosphatase is evidently of very rare occurrence. This presumably means that the production of testicular hormones required for establishing a normal production of phosphatase is smaller than that necessary to bring about normal androgenuria. This assumption is confirmed by the observations during treatment with chorionic gonadotropin, see Chapter XIX.

It is therefore reasonable to suppose that the production of phosphatase reaches the normal at a somewhat earlier stage of sexual maturation than does androgenuria. The present series of normal persons during puberty (Table XI, section 1) is comparatively small. The age limits within which the production of phosphatase reaches the values normal for adults can therefore be given only as a rough estimate. The limits will be about the 13th and 17th year, respectively (see Table XIX). In Hamburgers series (1948), androgen excretions above or equal to 20 I.U. per 24 hours (minimum figure for normal, middle-aged men) appear, at the earliest, at the age of 14, and

figures below 20 I.U. are found not later than at the age of 19. The age interval during which the phosphatase concentration reaches the normal for adult men thus appears to be earlier than the interval during which normal androgenuria is attained.

Development of Carpus and Production of Phosphatase.

A correlation is also found between these two sex characters, since a normal production of phosphatase does not occur until the development of the carpus has reached a degree corresponing to the age of 13 to 14 years. It further appears from the table that a carpal development corresponding to the age of 16 years or more will almost invariably be accompanied by a normal production of phosphatase.

Age and Production of Phosphatase.

The table shows that a normal production of phosphatase in normal and intellectually inferior boys may, in a few cases, be observed already at the age of 13. The influence of age in the other groups is dealt with below.

Group B. Hypandrogenic Boys and Men, previously treated with Sex Hormones.

As shown by Table XVII, this series of patients previously treated with sex hormones presents chiefly the same relations between the phosphatase concentration and the other accessory sex characters as were demonstrated in the series of previously untreated persons. In 3 (Nos. 12, 41, and 189) out of the 19 persons with normal phosphatase concentrations but with hypandrogenic terminal hair (degrees 1 to 3) there has, at a later stage, been demonstrated a fall to subnormal phosphatase concentrations, with the gradual subsiding of the effect of treatment (see Fig. 24); and in several of the remaining 17 the last treatment has been discontinued so short a time before the expression was performed that during a later period without treatment the phosphatase concentration would probably have been found to be lower in some of them.

Among the 5 persons without production of secretion, 3 (Nos. 18, 36 and 69) are remarkable in that they have no spontaneous production of phosphatase (see Fig. 24), despite repeated treat-

ment. The examinations were performed during a period without treatment when the production of phosphatase had again ceased, whereas pubes — and, in No. 69, also hirci — remained as almost irreversible signs of the imitation of puberty produced by treatment (see also Chapter XVIII). In yet another person (No. 55), examined after the first series of chorionic gonadotropin injections, the production of phosphatase had also

Table XX

Concentration of Phosphatase and Year of Life in treated and untreated Individuals.

Level of Phosphatase Concentration	Untreated — Year of Life									Treated — Year of Life									
	<11	11	12	13	14	15	16	17	≧18	<11	11	12	13	14	15	16	17	≧18
Infantilismus primarius.																			
"0"	—	—	—	1	1	3	1	—	1	—	—	—	—	—	—	—	—	—	—
<1	—	—	—	—	1	—	2	—	1	—	—	—	—	—	—	—	1	—	—
1-<5	—	—	—	—	—	—	1	—	1	—	—	—	—	—	—	—	1	—	—
5-<10	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	1	—	1	1
≧10	—	—	—	—	—	—	—	1	2	—	—	—	—	—	—	—	—	—	2
Infantilismus secundarius.																			
"0"	—	—	—	—	—	1	—	—	2	—	—	—	—	—	—	1	—	1	
<1	—	—	—	—	—	1	—	—	—	—	—	—	1	—	—	—	—	1	
1-<5	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	
5-<10	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	
≧10	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	
Pubertas tarda. Eunuchoidismus.																			
"0"	—	—	—	—	—	—	1	2	—	—	—	—	—	—	—	—	—	—	2
<1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	2
1-<5	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	2
5-<10	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	1	5
≧10	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	**5**
Dystrofia adiposo-genitalis.																			
"0"	—	1	3	1	—	—	—	—	—	—	—	—	—	1	—	—	—	—	
<1	—	—	—	2	1	—	2	—	—	—	—	—	1	—	—	—	—	—	
1-<5	—	—	1	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	
5-<10	—	—	—	—	—	—	—	—	—	—	—	—	—	—	2	—	1	2	
≧10	—	—	—	—	1	—	—	—	—	—	—	1	—	1	—	—	—	8	
Normal individuals during puberty.																			
"0"																			
<1	—	—	—	1	—	—	—	—	—										
1-<5	—	—	—	—	1	—	2	—	—										
5-<10	—	—	—	1	1	1	—	—	1										
≧10	—	—	—	—	—	—	3	1	1										

ceased, but subsequent treatment resulted in a lasting production of phosphatase.

Correlation of Phosphatase Concentration to Age in Untreated and Treated Persons.

Table XX shows the connection between these two factors. It maybe noted that the great majority of untreated cases of adiposogenital dystrophy have a subnormal production of phosphatase, in contrast with the treated patients. It is not permissible to conclude from the present series that the treatment has improved the production of phosphatase in this affection, since the treated patients with a normal production of phosphatase are mainly to be found in age-groups in which untreated patients are not represented.

Each of the groups of primary infantilism, secondary infantilism, retarded puberty and eunuchoidism presents, in the main, the same age distribution in the untreated and the treated section of the series; a comparison (see Table XX) does not support the theory that the normal phosphatase concentrations in the last-mentioned group are caused by the treatment, as the table shows the concentration to become normal at corresponding ages in the two sections. Comparison between the group of untreated patients and the material of normal persons shows that the spontaneous production of phosphatase in these patients sets in with a few years' delay.

Group C. Imbecile Boys during Puberty.

This series (Table XVIII) presents the same picture as was found in the untreated and treated series.

Table XXI gives the accessory sex characters that develop alongside with the production of phosphatase; limits are stated for incipient and normal production of phosphatase, respectively. By way of comparison the corresponding age limits for normal and for mentally inferior patients are shown. These limits, which are only directive, overlap with regard to some features, e.g. some individuals with beginning hirci may produce normal quantities of phosphatase, whereas the production has not commenced in others.

By way of conclusion it may be stated that the phosphatase concentration becomes normal at quite an early stage

Table XXI

Development of Sex Characters when the Production of Phosphatase begins, respectively becomes normal.

	Production of phosphatase begins at the earliest		at the latest	Production of phosphatase beromes normal at the earliest		at the latest	
Diameter of penis:	15	—	25	20	—	30	mm
Length of penis:	20	—	60			≧ 50	mm
Pubic hair:	1	—	3	2	—	4	
Terminal growth of hair:	0	—	2	1	—	4	
Prostate:	1	—	4			≧ 2	
Appearance of expressed secretion:	1	—	2	3	—	4	
Androgenuria:	0	—	10	0	—	20	I.E.
Carpal bone age:	11	—	13	13	—	17	years
Year of life: (normal individuals + imbeciles)	12	—	15	≦ 13	—	17	years

With regard to the estimation of the intensity of the sex characters, see page 49.

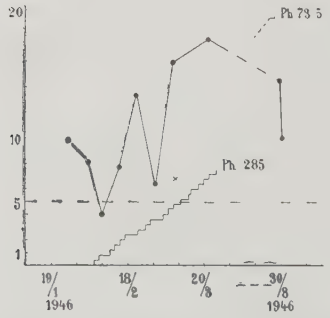
Figure 17.

Concentration of Phosphatase in the Course of Treatment with Chorionic Gonadotropin of a Eunuchoid with a Concentration of Phosphatase that was normal in advance.

Ordinate: concentration of phosphatase in K.P.U.

See also explanation in text, page 81.

Single dose (Physex): 1500 I.U.



No unquestionable effect of treatment on concentration of phosphatase.

of sexual maturation. The question is, then, whether the production of androgens reaches its maximum at the same time. The

following experiments may elucidate this point. In a single case the chorionic gonadotropin treatment of a eunuchoid (No. 64, Fig. 17) with a normal phosphatase concentration was carried out with control examinations of the phosphatase reaction. There was no definite increase of the phosphatase concentration, despite improvement of the other accessory sex characters; thus, the phosphatase concentration spontaneously achieved must be considered the maximum obtainable in this individual. As the treatment, on the other hand, caused improvement of the other accessory sex characters, it may be concluded that a normal phosphatase concentration (production of phosphatase) does not exclude a subnormal production of testis hormones.

One group of the series — **hypoplasia testis** — may be mentioned in fuller detail (see Table XXII).

All 9 persons examined produce normal quantities of phosphatase, despite volumes of testes down to even 1.5 ml (corresponding to the volume of two spheres, each with a diameter of 1.1 cm) which is 6 per cent. of the normal average volume. It may be mentioned for comparison that Sand (1918), and Lipschütz and Ottow (1920), by testicular transplantation and partial castration, respectively, succeeded in producing, respectively maintaining, the accessory sex characters to a normal extent, with volumes of the testes down to a few per cent. of normal volumes.

Abnormal decrease of the volume of the testes is very frequently accompanied by hypoplasia or atrophy of the spermatogenic tissue (Olesen, 1948). As this constitutes by far duals with aspermia or a considerable degree of reduced fertility, the greater part of the volume of the testes, it is obvious that a considerable reduction of this tissue may reduce the volume of the testes considerably, without simultaneously reducing the total volume of the Leydig cells. Further, the examination of the phosphatase concentration in ejaculated semen from individuals with aspermia or a considerable degree of reduced fortility, as mentioned on page 39, shows that severe lesions of the exogenic tissue of the testes need not exert an influence on the production of testis hormones which will manifest itself in the production of phosphatase. Aspermia was ascertained in the

Table XXII

The Concentration of Phosphatase and other Properties in 12 Patients with small Testes but with normal terminal Growth of Hair.

No.	Concentration of phosphatase in K.P.U. in first expressed secretion	in second expressed secretion	Volume of testes in ml	Diameter of penis in mm	Lenght of penis in mm	Androgen uria in I.U
						Previously
106	6.4	—	8.2			40
179	7.4		6.5	25	71	
76	9.3	6.6	5.0	24	75	45
78	11.0	11.0	6.2	23	87	35
144	12.3	10.9	1.5	26	96	7
47	13.1	9.0	7.8	23	50	6
45	13.9	7.6	ca. 7			
142	14.3	16.3	3.7	27	67	25
9	15.7	16.3	ca. 7			
53	18.5		2.6	23	82	62
						Previously
316	7.2	3.4	5.7	23	79	30
33	10.5	3.5	ca. 5	20	60	

three patients who had the lowest volume of testes (Nos. 53, 142 and 144).

However, the fact that the 9 patients include 2 with hypandrogenuria supports the view that a slight reduction in the production of testis hormones may be present despite the fully virile apparation. This is further indicated by the late onset of puberty in 2 patients (Nos. 76 and 179) and the eunuchoid pro-

Height in cm	Height when sitting	Weight	Age	Parotitis previously (++: orchitis)	Gonorrhoea previously	Children	Puberty began in year of life	Comments
ıntreated.								
173	84	74	50.4	—	+	2	norm.	Gastritis
167	84	77	59.10	—	-	1	16-17	Arthritis urica
168	82	66	38.11	+	+	2	20	Neurosis cordis. Torticollis
168	83	63	40.9	±+	—	0		Ulcus duodeni
161	80	61	35.0	—		0		Aspermia, gynæcomasti, surdomuditas
			49.6					
159		58	23.9	—			norm.	
171	83	91	30.4	—		0		Aspermia, hypometabolismus, adipositas of "Fröhlich-distribution"
			29.11				10	Adipositas l. g. of "Fröhlich-distribution"
173	81	74	24.9	+			15	Aspermia
reated.								
			31	—		0	14	Adipositas l. g. diffuse distribution
			59.0					Adipositas l. g. of "Fröhlich-distribution"

portions in 2 others (Nos. 53 and 106. It is remarkable that one (No. 144) had gynaecomastia, and three (Nos. 9, 33 and 142) had "Fröhlich's distribution" of the subcutaneous fatty tissue.

Group D. Impotentia coeundi (Table XXIII).

This group comprises patients with a more or less impaired

Table XXIII

The Concentration of Phosphatase and other Properties in 22 Patients suffering from Impotentia coeundi but with no somatic hypandroid Features.

No.	Concentration of phosphatase in K P.U. in first expressed secretion	in second expressed secretion	Log c. o. p. in first express. secret.	Admixture of urine in per cent	Andrinuria in I.U.	Volume of testes in ml§)
114	1.9	1.2	0.28	(0)*)	16	23.8
111	5.0		0.70	2		19.8
140	5.2	3.3	0.72	0	12	23.9
110	6.4	—	0.81		7	46.3
159	7.4	—	0.87	0	53	33.0
107	10.3	7.8	1.01	26	32	17.8
116	10.6	13.3	1.03	20	27	c. 20
161	10.8		1.03		16	23.2
184	10.8	11.2	1.03	0	28	21.9
181	11.4		1.06	0		30.8
14	12.2		1.09			n.
2	12.6	10.1	1.10		3	n.
6	14.1	9.4	1.15			n.
40	14.5	14.9	1.16			24.3
31	15.1	15.7	1.18			n.
178	15.3		1.18	2		23.3
109	15.6	4.0†)	1.19			17.2
182	16.4		1.21	6		27.2
30	17.8	17.2	1.25			c. 19
27	18.1	21.4	1.26			n.
17	18.9	15.0	1.28			n.
15	22.9	10.2⁰)	1.36			n.

⁰) Expressed secretion obtained few hours after an ejaculation.
*) First expressed secretion not examined for urine. Admixture o urine never demonstrated in numerous examinations of sub sequent expressed secretions.
†) Admixture of urine 56 %.
§) An n in this column means that on palpation the testes were est mated to be of normal volume.

copulative function: failing or brief erection, failing orgasm, ejaculatio praecox, absent or considerably reduced libido — all without accompanying somatic hypandry. This last-mentioned limitation of the series goes against a reduced androgen production as the cause of the affection. As already mentioned, determinations of the phosphatase concentrations might, however, reval decreases in the androgen production of so short

Age	Duration of disease in years-months	Gonorrhoea antea	Comments
51.7	0.3		
39.8	?		
56.8	1.6		Strumectomia in 1942 (4 years ago).
34.0	2		
46.1	0.9	—	
45.10	0.6	—	
52.2	3		Polyarthritis urica.
51.10	0.6		
48.10	10	—	Gonorrheal prostatitis in 1924. Prostate slightly nodose. No leukocytes in expressed secretion.
46.5	6	—	
35.0	?		Chronic hepatitis. Depressio mentis psykogenica.
31.0	0.4		Beard growing more slowly during last 4 months.
45.11	0.1		Sinus bradycardia. Exstra systoles.
35.7	0.6		
28.10	7		Slight prostatism.
36.11	c. 2	—	
43.5	2		
33.9	0.8	—	Hypertensio arterialis l. g.
58.8	4		Nycturia. Prostate normal.
40.3	9		Nervosismus. Hemicrania.
34.0	?		Previously treated with testosterone. Myocarditis subacuta, Extra systoles.
52.11	?		Varicocele sin. m. g.

duration that they would not manifest themselves in the other somatic sex characters.

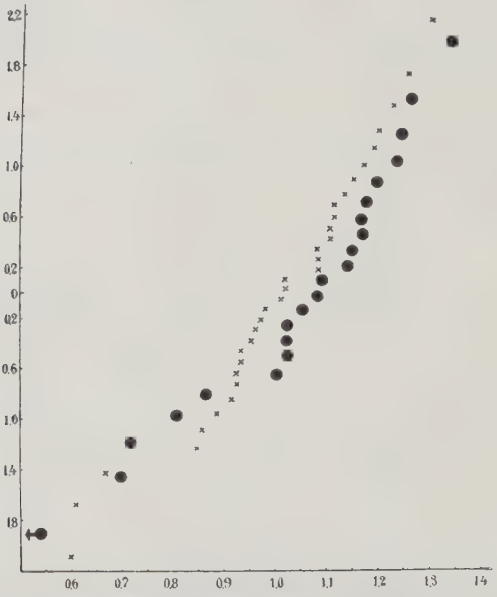
In Fig. 18 the cases have been plotted in a rankit diagram in addition to the normal series from which they differ in that the logarithm of the phosphatase concentration shows uneven distribution with accumulation of low values.

It thus appears that the impotent patients include some with

Figure 18.

The Concentration of Phosphatase in 22 Patients suffering from Impotentia coeundi (●) and in 33 normal, middle-aged men (×), cf. Fig. 12.

Abscissa: log concentration of phosphatase.
Ordinate: rankits.



The irregular distribution of the concentration of phosphatase of the impotent patients may be supposed to be due to a decreased production of testis hormone in some of them.

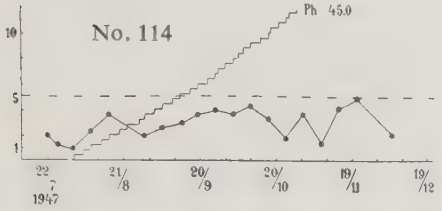
a slight reduction of the production of androgens in spite of normal, virile development of the somatic sex characters. It appears from Table XXIII that there is a remarkably high number of patients with subnormal andrinuria, a fact that confirms H a m b u r g e r's observation (1947). He found the renal androgen excretion in impotent persons to be below 20 I.U. in the 24 hours in many cases.

In a single untreated person (No. 114), who suffered from a mild degree of impotence of fairly short standing, a very low phosphatase concentration was ascertained. Treatment with chorionic gonadotropin (see Fig. 19) was only of uncertain effect on the phosphatase concentration, which never reached normal figures. Testosterone treatment might possibly have revealed which organ — the testes or the prostate — was the

Figure 19.

Patient suffering from Impotentia coeundi with decreased Production of Phosphatase, treated with Chorionic gonadotropic Hormone.

Ordinate: Concentration of Phosphatase tn K.P.U.
See also explanation in text, page 81.
Single dose of Physex: 1500 I.U.



The production of phosphatase remained uninfluenced by chorionic gonadotropin.

cause of the low phosphatase concentration; but is was not administered.

Group E. Gynaecomastia.

Previous Authors.

In the affections in which this symptom occurs, a hormonal imbalance may be supposed to exist; thus, during puberty in otherwise apparently normal persons, and in adiposogenital dystrophy, in cirrhosis of the liver (deficient destruction), in treatment with oestrogen, in cancer of the prostate, (Waldenström, 1948), in leprous orchitis (Maxwell), as a consequense of insufficient prison diet (Hibbs, 1947), in Klinefelter, Reifenstein and Albright's syndrome (1942), and in Heller, Nelson and Roth's syndrome (1943). The hormonal causes of gynaecomastia are yet uncertain; this question will not be discussed in fuller detail here.

If gynaecomastia is indicative of a considerable degree of "devirilization", it may be supposed to be accompanied by a lowered phosphatase concentration.

Writer's Examinations.

In 4 persons (Nos. 47, 105, 127 and 187; see page 141) with this affection, the phosphatase concentrations were determined. Patients with adiposogenital dystrophy and tumours of the mammary glandular tissue are not included. In No. 105, a man aged 20, the concentration was 10.3 K.P.U.; the volume of the

testes was 18.7 ml; andrinuria 36 I.U. The somatic sex characters were found to be fully virile. Gynaecomastia set in simultaneously with the onset of puberty, about the age of 15.

The phosphatase concentrations in this series were not below values that might be explained by the ages of the patients. In this connection it must be mentioned that the oestradiol treatment, mentioned on page 97, caused slight gynaecomastia without reduced production of phosphatase. Thus, a normal production of phosphatase does not exclude the presence of oestrogenic substances in the organism, in quantities sufficient to produce gynaecomastia.

In Nos. 105, 127 and 187, the growth of the mammary glands began during puberty which otherwise followed normal course and, in No. 105, aged 20, has now been completed. In No. 47, aged 49, in whom the phosphatase concentration was found to be 13.1 (at the next expression 9.0) K.P.U., the somatic sexual maturing is complete, but the testes are too small (7.8 ml), and the andrinuria is reduced (6 I.U. in the 24 hours).

Chapter XVI

SEXUAL MATURATION AND ITS MECHANISM IN BOYS. PREVIOUS INVESTIGATIONS

Spontaneous Puberty.

The growth of the penis is only slight up to the age of 9 or 10 years. The volume of the testes remains at 1.5 ml (Roessle and Roulet, 1932; Reich, 1924). During this early period, the prostate doubles its weight from about one to about two grammes, and, microscopically, there is an increase in the number of acini, the epithelium of which remains low cuboidal without signs of secretion and with narrow lumina (Moore, 1936 b).

About the age of 9 or 10 years the first signs of sexual maturation appear; the volume of the testes increases; histologically the prostate shows signs of activity; during the years that follow, the acini grow more numerous and rounded, with increasing lumen; and the epithelial cells become more prominent with a distinct zone of cytoplasm between the nucleus and the lumen, but still without any secretion. The final ability to function, Moore assumes, is attained in the course of a few weeks or months. Further, an increased excretion of sex hormones in the urine can be observed. The renal excretion of andrin and oestrin remains low until about the age of 7, when both are slightly increased, the excretion of andrins to a somewhat greater extent than that of the oestrins. From about the age of 9 there is a slight increase of the excretion of andrin, ascertained by photometry. It is considerably increased after the age of 11 (Nathanson, Towne and Aub, 1941). In Engberg's series (1948; ascertained by biometry) comprising 65 boys

between the ages of 8 and 18, there is an initial increase about the age of 12, and a distinct increase at 14. By means of biometry, Pedersen-Bjergaard and Tønnesen (1948) found a demonstrable excretion of androgens in boys already from the age of 8. This excretion increases slowly during the following years, rising considerably after the age of 15.

A demonstrable excretion of oestrin is found from the age of 10 (Eng, 1937). Between the ages of 10 and 17, the oestrinuria is observed mainly in boys showing distinct signs of sexual maturation.

Barely demonstrable quantities of follicle-stimulating hormones in the urine do not appear until about the age of 13, according to Nathanson, Towne and Aub (1941), whereas Pedersen-Bjergaard and Tønnesen (1948), with their better technique, were able to demonstrate a measurable excretion from the age of 8. By means of Evan's method, Freed (1935) was able to demonstrate small quantities of "prolan" in the urine already from the ages of 4 to 5 years. The excretion of gonadotropin increases evenly up to the age of 15, and then remains constant until senility. In 1938 Catchpole, Greulich and Sollenberger found that 18 completely infantile boys under 12, had a renal excretion 2 M.U. of gonadotropin in the 24 hours. Nor did 4 out of 15 boys between the ages of 12 and 16 produce any gonadotropin, whereas the excretion in the remaining 11 boys was between 2 and 10 M.U. in the 24 hours.

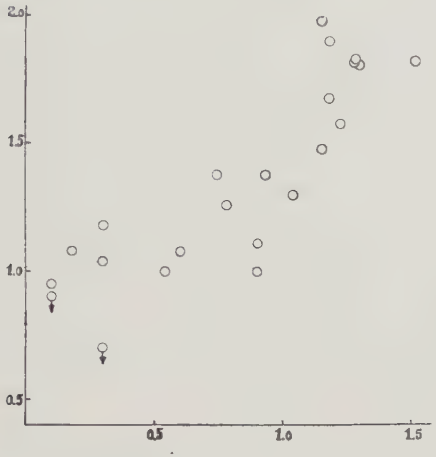
In 9 out of 12 boys between the ages of 11 and 15, inclusive, Hamburger and Halvorsen (1942) found no gonadotropin in the urine (there were traces in one case, however), whereas in the remaining 3, there were excretions of 17 R.U. or more in the 24 hours — a fact which they considered indicative of an increased hypophyseal activity during puberty. In 6 out of 61 boys aged between 8 and 18 Engberg (1948) found gonadotropin excretions of 17 R.U. or more in the 24 hours.

Somatically, puberty sets in with accelerated growth of the testes and penis. Roessle and Roulet (1932) computed the average weight of the testes in the age-group 13 to 17 years to be 20.6 gm. The weight of the prostate simultaneously increases to about 8 gm. (Roessle and Roulet), growth of terminal hair appears, etc. The time of onset of puberty varies

Figure 20.

The relation between the interdependent values found by Dorfman, Greulich & Solomon (1937) for the excretion of andrin and oestrin in the urine of 18 boys from the 6th to the 16th years of life inclusive.

Abscissa: log content of andrin in I.U.
Ordinate: log content of oestrin in I.U.



greatly. A clinically suitable criterion for the onset of puberty is afforded by the appearance of the pubic hair which, in Schonfelds series (1943) comprising 1,475 normal boys, came out between the ages of 11 and 16, both ages inclusive.

Moreover, as the rate of the processes of puberty varies considerably, it is easy to realize that, between the ages of 12 and 16, there is only a slight correlation between the actual age and the degree of development of the sex characters. Greulich *et al.* (1942) particularly stress the "physiological age", giving five "maturity groups" which are mainly characterized the sizes of the testes and the penis, and by the growth of terminal hair. These writers find a better correlation between the degree of maturity, on the one hand, and the epiphyseal development, the excretion of andrin and oestrin, on the other hand, than between the actual age and these qualities. Their series of cases was too small for a demonstration of any significantly greater correlation to be made — though this probably exists — between the degree of maturity and gonadotropinuria than between actual age and gonadotropinuria.

A tabulation of the values found by Dorfman *et al.* (1937)

for the excretion of andrin and oestrin in 18 boys aged 6 to 16, inclusive, is made in Fig. 20, which shows good mutual correlation between these two sex characters.

According to Greulich *et al.* (1942), the sequence in which puberty manifests itself in the most essential clinical sex characters is a follows: —

(1) Growth of the testes and penis. The testes frequently become softer during this rapid growth. The penis first grows longer, then thicker.

(2) Downy pubes.

(3) Scanty long and straight pubes at the base of the penis.

(4) Dark down laterally on upper lip ("moustache").

(5) Perianal pilosity.

(6) Denser, curly pubes with concave or straight upper edge, and sharply defined laterally.

(7) Hirci, beginning at the latest one year after first appearance of pubes. Normal density of hirci attained in the course of another year.

(8) Voice breaking.

(9) Testes and penis of adult appearance; hair appearing along the linea alba: the first virile hair on the body.

(10) Appearance of stiff barbae.

This sequence is almost always observed in normal persons. Among 476 boys, Greulich *et al.* (1942), found only 3 with breaking voice before the appearance of the pubes; and in only 2 did hirci appear before the pubes.

Special mention may be made of the increase in volume of the testes during puberty. With and From Hansen (report to be published), using the same methods as in the present works, ascertained the following volumes of testes (in millilitres) in normal boys under the age of 15:-

Ages	Minimum Volume ml.	Maximum Volume ml.	Average Volume ml.	Number of Boys Examined
7th to 9th year of life	0.7	1.9	1.4	14
10th — —	1.8	2.0	1.9	2
11th — —	1.3	4.2	2.5	4
12th — —	1.0	6.8	3.9	9
13th — —	3.1	11.4	6.1	10
14th — —	4.0	17.4	8.0	8

According to Hurxthal (1947), volumes below 2 ml before puberty should arouse the suspicion of hypogenitalism. According to the axaminations be With and From Hansen this is only the case after the age of 13. As appears from the table, the volume of the testes has, in some cases, increased considerably already by the age of 11, and in all cases before the age of 14. The same limits were found by Schonfeld (1943) in a greater series.

Under the thirteenth year, the normal lower limit, according to With and From Hansen's investigation, is about 1 ml.

Early Onset and Rapid Course of Puberty.

Besides the extreme cases of pubertas praecox, there is a group of boys who are characterized by Werner, A. A. (1942) as short and strongly built, in whom puberty sets in at a somewhat earlier stage, thoug within the normal age limits; its course towards completion is rapid, the epiphyses close early, and the extremities are short in relation to the trunk. According to Kubitschek (1932), puberty commences earlier in boys of an athletic build than in asthenic boys. Richey's (1932) criterion is the growth of hirci, and he found that boys with earlier onset of puberty are taller and heavier than boys in whom puberty begins later. The "sexually mature dwarfs" described by Horstmann (1949) seem to be very much like Werner's type described above. Bruch (1941) examined 110 obese boys, without intracranial lesions or endocrine disturbances, in whom adipositas had developed before the onset of puberty. Even before puberty, these boys were taller than the normal for their age, and the epiphyseal maturation was several years ahead of their actual ages; puberty in these boys set in somewhat earlier than normal. In all, the growth of the genitals began before the age of 14, and the age distribution during the stage of fully virile pubes, of hirci and moustache, reached the same maximum as in normal cases, but the distribution in relation to the latter was irregular, with preponderance in the younger age groups. It seems as if the five cases described by Hanssen (1937) as being of a "special type" of adiposity during adolescence must be considered extreme variants of this type of boy.

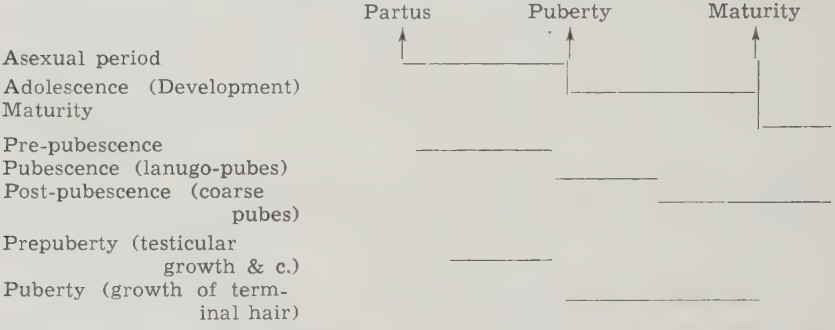
Delayed Onset of Puberty.

The extreme limit of late onset of spontaneous, normal puberty, judged by the appearance of pubes, must be fixed at the end of the sixteenth year, according to Greulich *et al.* (1942), Schonfeld (1943), and Werner, S. C. (1941).

Th causes of infantilism also incolve delayed puberty in many cases, but there seems to be no avaiable reports of how late spontaneous puberty may set in in patients with infantilism.

Various Mechanisms of Sexual Maturation. Terminology:

The various terms used to describe the development in relation to the sexual maturing were defined by Crampton in 1908; his definitions are still used, thus by Richey (1937). They appear from the following diagram:



This terminology deviates from the Danish usage, where the term "prepuberty" is used for the period between the ninth to tenth years and the beginning of sexual maturing; also, the word "puberty" is not used about a definite time, but about the period which Crampton calls "adolescence", or rather the period from the beginning of pubescence to maturity. In the present work, "puberty" is used to denote this latter period, but it is mainly reserved for the sexual maturing due to spontaneously lasting production of testis hormones; this production may, then, have begun spontaneously or have been provoked by treatment with gonadotropin. According to this definition, the sexual maturing caused by testosterone is not puberty, since it ceases when the treatment with testosterone is discontinued. Such temporary development of the sex characters will described in the following as sexual maturing by testosterone.

Whereas the functions of the pituitary and the testes are without any importance to the attainment of sexual maturing by testosterone, a stimulation of the testes is a necessary condition for the establishment of sexual maturation by gonadotropin. During intensive treatment with gonadotropin the condition of the pituitary is presumably of no consequence to the development of the sex characters.

After discontinuance of treatment, the processes will either stop or progress. In the former case, the result obtained may be described as imitation of puberty which is similar to sexual maturing by testosterone in that the development will stop simultaneously with the discontinuance of treatment, and only differs in that it is the organism itself that supplies the testosterone as long as its testes are influenced by the administration of gonadotropin.

But if the sexual maturing processes once started continue, despite discontinued treatment, the organism has entered the stage of puberty and the proper term for this state will be: provoked puberty.

It appears that previous authors have not taken up a definite view as to whether sexual maturing by gonadotropin is imitated or provoked puberty. The latter construction seems to be tatken for granted by, amongst others, C. R. Moore (1939) who states that treatment with gonadotropin is able to produce precocious puberty as early as between the ages of 5 and 10 years — without any reserve as to whether the sex characters produced will progress or stagnate after discontinuance of treatment.

Thompson and Heckel (1939) express themselves with reserve: "genital growth produced by this material (i.e. gonadotropin) may be so marked that changes simulating premature puberty result". Thompson *et al.* (1938) did not observe signs of premature sexual maturing until after 9 weeks' treatment. In a boy aged 7, six months' treatment resulted in vigorous growth of pubes and downy barbae. In only half of the children treated there was growth of the genitals, and in a number of them the changes subsided after cessation of treatment.

An analysis in advance of the problem would lead to the conclusion that gonadotropin treatment of normal boys during childhood only results in imitation of puberty, since chorionic gonadotropin is not known to produce any increased — let alone

any permanently increased — production of gonadotropin by the pituitary gland. The results ascertained by Finkler *et al.* (1942) in boys suffering from cryptorchidism, hypogenitalism and retarded growth treated from ages as low as 1 year, also support the supposition that chorionic gonadotropin may well cause imitated, but not provoked, puberty during childhood. The authors discontinued treatment if the development of the genitals exceeded the limits normal for the actual age of the boys in question, after which further progression was not observed, in spite of the fact that large total doses were administered: up to a total of 131,200 I.U., over two years, in a boy aged 4. Moore (1939) maintains that infants may develop a growth of terminal hair during gonadotropin treatment — which has not been observed by Tager (1942).

The reaction of a normal boy to chorionic gonadotropin may perhaps be a provoked puberty rather than imitation of puberty — if treatment is instituted during prepuberty when the hypophyseal production of gonadotropin is higher than during childhood.

Truly, the present work does not include examinations of treatment of normal boys. Patients with adiposogenital dystrophy will, as described in the following, almost invariably attain provoked puberty during prepuberty, whereas, in many cases, only imitation of puberty is obtained in patients within the group of infantilism — at any rate with the first courses of treatment with chorionic gonadotropin.

Chapter XVII

WRITER's EXAMINATIONS OF THE DIFFERENT FORMS OF PUBERTY BY MEANS OF THE PHOSPHATASE REACTION

In the following the different forms of puberty (definition, see page 177) will be discussed: Spontaneous puberty, provoked puberty, and imitation of puberty as well as combinations of these such as they occur in a series of patients, who have been followed through a prolonged period, have been periodically untreated, or during other periods treated with chorionic gonadotropin.

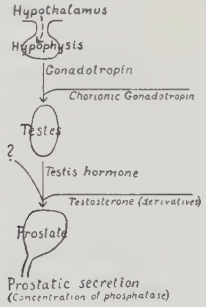
As was shown in the preceding pages, a distinction between these forms of sexual maturation has been rendered possible by the phosphatase analyses for, in contrast with criteria such as growth of terminal hair and epiphyseal maturation the production of phosphatase closely follows the testis hormone production and is fully reversible, and has proved to be of a suitable sensitiveness to testosterone. The diagram, Fig. 21, illustrates the assumed relations between the hypothalamus-pituitary, testes and possibly other relevant endocrinous glands on the one hand, and the production of phosphatase on the other hand as well as the point of aggression of the sex hormone therapy.

A. Spontaneous Puberty in Untreated Individuals.

Fig. 22 shows the spontaneous course of the production of phosphatase in puberty, and that this production is brought about rather slowly. It lasts several months before the production of a secretion without phosphatase is replaced by a production of the enzyme, and another long period passes before the

Figure 21.

Diagram showing the target organs of the various Hormones and Hormone Preparations stimulating the Production of Phosphatase.



production of phosphatase becomes normal. Thus Moore's assumption (1936 *b*), based on histological findings, that the complete functional efficiency of the prostate was reached within a few weeks or months, does not hold good in the case of the production of phosphatase. Further, there is a marked difference in this spontaneous torpid start of the production of phosphatase and the more explosive start during the treatment with chorionic gonadotropin (see below).

B. Sexual Maturation caused by Chorionic Gonadotropin: Imitation of Puberty or Provoked Puberty.

The aim of the following examinations of the reaction of the production of phosphatase to chorionic gonadotropin treatment is to determine to how great an extent the testes in hypandrogenic individuals may be stimulated to further activity, and to what extent this stimulation effect is of a permanent character.

As was shown in Chapter XII, the spontaneous production of phosphatase affords information about the actual androgen production, part of which originates from the testes. The production by the testes depends, among other things, upon the intensity of the stimulation to which they are exposed. If the variations in this factor are eliminated by the testes being exposed to a maximum stimulation, the ensuing production of phosphatase must afford some information about the potential efficiency of the testes for hormone production.

There are three necessary conditions for this conclusion: The treatment must really bring about a maximal stimulation of the

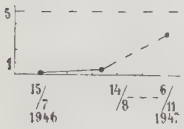
Figure 22.

Spontaneous Course of the Concentration of Phosphatase in 5 Boys during the beginning of puberty.

Ordinate: Concentration of phosphatase in K P.U.
See also explanation in text page 81.

No. 80

No. 108



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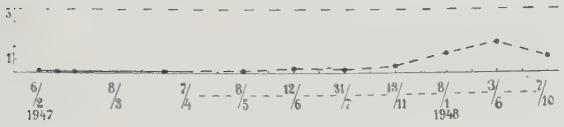

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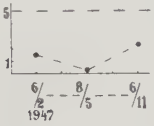
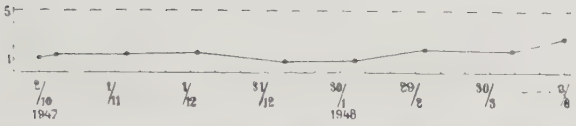


No. 187



Compared with the course during treatment with chorionic gonadotropin (see Fig. 24) the concentration of phosphatase shows a very slow rise.

testes, it must stimulate the testes electively, and the prostate must be able to respond to the testis hormone with a production of phosphatase.

To settle the first of these questions, five patients (Nos. 79, 149, 153, 165 and 170) were treated with doses still larger than the 1500 I.U. of chorionic gonadotropin which has been the

dosage generally applied in the experiments, and to which these five patients had responded with a submaximal production of phosphatase. The results recorded in Fig. 24 show that only No. 79 attained a further (moderate) rise of the phosphatase concentration by the more intensive treatment, which was without further effect in the remaining four patients. These experiments thus indicate that an increase of the dose above 1500 I.U. 3 times a week very seldom will bring about a further increase of the production of phosphatase.

That does not mean, however, that a maximum stimulation of the testes can be obtained at all with chorionic gonadotropin. But as the attemps at causing a production of phosphatase with equine gonadotropin (which is of hypophyseal origin) failed. it may be justifiable to assume that it is impossible to obtain any great stimulation of the testes by any known hormone or hormone preparation.

The second condition, that the treatment must exert an elective stimulating action on the testes seems to hold good, when chorionic gonadotropin is applied. First, S m i t h (1926—27) and M o o r e *et al.* (1937) found that the prostate of castrated animals is not affected by gonadotropin, and, secondly, F r a s e r *et al.* (1941) have demonstrated that the 17-ketosteroid excretion in castrates and certain eunuchoids is not increased by treatment with gonadotropin. A stimulating influence on the possible androgenic production of the adrenal cortex or other non-testicular glands is thus apparently not exerted by the preparations.

The third necessary condition that the prostate must be able to respond to testis hormone is also complied with, as shown on page 86, although there are great individual variations in the response of the prostate to the administration of testosterone.

SURVEY OF THE SERIES OF PATIENTS, AND RESULTS

The preparation administered was Physex Leo (chorionic gonadotropin), generally in single doses of 1500 I.U. injected intramuscularly 3 times a week, as a rule in courses each of about thirty injections.

The Phosphatase Concentration before, during, and after the first Course of Chorionic Gonadotropin Injections.

Table XXIV shows the effect on the phosphatase concentration

of the first course of treatment with chorionic gonadotropin in previously untreated hypandrogenic individuals. Each of the 4 reactions registered in the table illustrates the function of the testes and the prostate of the patient. The initial phosphatase concentration (column 2) indicates the spontaneous androgen production, the latent period (column 3) conveys an idea of how far the testes (and the prostate) are from functioning or from increasing function, i. e. how undeveloped they are; the phosphatase concentration during the treatment (column 4) shows the functional efficiency of the testes (and the prostate) in the course of massive stimulation, and, lastly, the phosphatase concentration after the treatment (colum 5) shows whether the result obtained during the stimulation period has been a temporary one (imitation of puberty), or whether the injected gonadotropin has had a permanent effect (provoked puberty).

It appears then from the table that nearly all the patients examined have reacted by starting the prostatic secretion or — mostly — by increasing the phosphatase concentration during the treatment. The imperfect reactions of Nos. 98, 128, and 174 are probably due to the treatment with chorionic gonadotropin having been too brief. The prompt effect of subsequent treatment with testosterone propionate in No. 174 shows that the prostate is able to respond. As the series comprises excessively severe forms of hypandry, e. g. Nos. 79 and 126, the conclusion may be drawn that the testes in previously untreated patients suffering from infantilism, pubertas tarda, eunuchoidism and dystrophia adiposo-genitalis will often respond to a treatment with chorionic gonadotropin of the mentioned intensity with a certain hormone production, at the latest in the third month of treatment.

Column 4 of the table shows, however, that only in the fewest (5 out of 24) patients the treatment with gonadotropin is capable of producing a normal phosphatase concentration ($>$ 5 K.P.U.), whereas one half of the rest is about the lower limit of the normal (5 K.P.U.), and the other half in the range between 1 and 5 K.P.U. However, in two of the patients (Nos. 170 and 174) a production of secretion only was obtained, and no phosphatase production of any importance, i.e. a phosphatase concentration $<$1 K.P.U.

The latent period — the time from the beginning of the treatment until an unquestionable increase of the phosphatase con-

Table XXIV

The Concentration of Phosphatase before, during and after first Series of Chorionic Gonadotropin in 25 previously untreated Patients with a subnormal Concentration of Phosphatase.

(The sequence is determined first by the initial concentration of phosphatase, since by the concentration produced).

No.	Initial concentration of phosphatase	Latent period in months. Concentration of phosphatase "0" → > 1	"0" → < 1	Concentration of phosphatase during treatment	after treatment
170	"0"		< 1	< 1	
174*)	"0"		< 1	< 1	
49	"0"	2-3	< 1	1-< 5	cessation
149	"0"	1-2	< 1	1-< 5	cessation
194	"0"	1-2	< 1	1-< 5	cessation
196	"0"	2-3	< 1	1-< 5	cessation
70	"0"	1-2		1-< 5	unchanged
123	"0"	about 1	< 1	1-< 5	?
79	"0"	2-3	< 1	about 5	cessation
126	"0"	about 1	< 1	about 5	cessation
97	"0"	1-2	< 1	about 5	fall → 1-< 5
191	"0"	< 1	< 1	about 5	fall → 1-< 5
193	"0"	1-2	< 1	about 5	fall → 1-< 5
119	"0"	1-2	< 1	about 5	unchanged
68	"0"	3	< 3	> 5	fall → about 5
192	"0"	1	< 1	> 5	unchanged
98*)	< 1			< 1	
54	< 1	1-2		about 1	cessation
35	< 1	about 1-2		about 5	unchanged
136	< 1	about 1		> 5	unchanged
66	about 1			1-< 5	unchanged
134	about 1	1[0])		about 5	unchanged
63	1-< 5			1-< 5	
74	1-< 5	< 1[0])		> 5	unchanged
164	1-< 5	1-2[0])		> 5	unchanged

*) Treatment discontinued too early.
[0]) Time passing until the rise is distinct.

Reaction type, cf. Fig. 23	Total dose of Physex in 1000 I.U.	Duration of treatment in months	Observed after treatment, in months	Diagnosis	Age
1	45.0	2 ½	1 ¾	Infantilismus primarius	15.2
1	25.5	1 ¼	3 ½	Dystrofia adiposo-genitalis	12.4
2 b	42.0	3	1 ½	Infantilismus primarius	16.9
2 b	45.0	2 ¾	3	Pubertas tarda	17.5
2 b	36.0	3 ¼	1 ¼	Infantilismus primarius	18.7
2 b	43.5	2 ¾	3 ½	Infantilismus primarius	13.6
2 a	45.0	2 ¾	22	Dystrofia adiposo-genitalis	13.8
2	30.0	1 ½	0	Infantilismus primarius	15.9
2 b	90.0	5 ¼	7 ½	Infantilismus secundarius	19.6
2 b	43.5	2 ½	9	Infantilismus secundarius	18.11
2 c	43.5	2 ¾	1 ¾	Infantilismus primarius	14.1
2 c	45.0	2 ¾	1 ¾	Pubertas tarda	16.3
2 c	43.5	2 ¼	4	Dystrofia adiposo-genitalis	11.9
2 a	67.5	4	12	Dystrofia adiposo-genitalis	12.1
3 c	43.5	2 ½	2	Dystrofia adiposo-genitalis	12.10
3 a	43.5	2 ¾	2	Infantilismus secundarius	15.3
	12.0	¾	0	Dystrofia adiposo-genitalis	14.3
2 b	31.5	1 ¾	2	Infantilismus primarius	16.1
2 a	31.5	2 ½	1 ¾	Dystrofia adiposo-genitalis	16.7
3 a	36.0	2 ¼	9	Dystrofia adiposo-genitalis	14.1
	42.0	2 ½	4 ½	Dystrofia adiposo-genitalis	16.0
	45.0	2 ¾	6 ¼	Dystrofia adiposo-genitalis	13.10
	50.0	4 ¼	9	Dystrofia adiposo-genitalis	12.8
	45.0	2 ¾	5	Infantilismus secundarius	17.5
	46.5	3 ¾	1 ¾	Pubertas tarda	19.1

centration appears (in cases in which the initial value is "0", the increase is considered to have commenced when the phosphatase concentration reaches above 1 K.P.U. — varies from about a fortnight to 3 months (column 3), being mostly between 1 and 2 months.

In the period immediately after the discontinuance of the treatment (column 5) the result obtained was lasting in nine patients only; four patients showed a decrease of the phosphatase concentration, which, however, remained higher than prior to treatment, and finally, seven patients showed a fall to pre-therapeutic conditions. In these latter patients the testes have thus not been able to function satisfactorily without an addition to the gonadotropin production of the pituitary.

Conclusion: —

With regard to the relation between the phosphatase concentration prior to, during and after the treatment with gonadotropin, it is seen that virtually all combinations do occur. With the necessary reservation because of the small number of patients, the following may, however, be inferred: —

Patients with undoubtedly lacking phosphatase concentration (initial value "0") vill respond more slowly to the treatment with gonadotropin than patients with a certain phosphatase concentration, and they will rarely reach a normal phosphatase concentration. If the beginning of the output of secretion (judged by the result of prostate massage) is chosen as a criterion of the effect of chorionic gonadotropin, the latent period is, however, not longer for the group of patients with the initial value "0" (see Table XXIV). The phosphatase concentration obtained does not predict anything certain about the subsequent course. Still, cessation of the phosphatase production has not been observed after a fully normal phosphatase concentration has been obtained. If there is a production of phosphatase before the treatment (phosphatase concentration about 1 K.P.U. or above), the effect produced is retained after discontinuance of the treatment.

The Phosphatase Reaction in Patients with initially absent Production of Phosphatase.

In the following the patients who prior to treatment were so

hypandrogenic that a production of phosphatase was absent or insignificant (initial value "0" or < 1 K.P.U.) will be mentioned separately. Treatment of such a patient with a course of chorionic gonadotropin injections will either exert no influence on the phosphatase concentration or bring about a certain, though subnormal, phosphatase concentration, or, as a last possibility, lead to a normal production of phosphatase. After discontinuance of the treatment there may for the two last-named courses be three possibilities, namely, the phosphatase concentration will either remain at the subnormal or normal level attained, or it will fall to a lower level and remain there, or it will decrease to 0, which means that the production of phosphatase has ceased again.

These differences in the course during the treatment with chorionic gonadotropin and thereafter are illustrated by the diagram, Fig 23, with additional examples from the series in Table XXV.

It will be discussed in the following to what extent it is possible from the response of the prostate to treatment with chorionic gonadotropin to make conclusions as to the function of the testes and on to that of the pituitary. To begin with, mention may be made of some of the observations, on which the conclusions are based: —

— As was shown on page 86, the testosterone treatment to which young, very hypandrogenic patients with lacking production of phosphatase are submitted, will start the production.

— Even a maximum stimulation of the prostate with testosterone is not always capable of producing a normal phosphatase concentration.

— A subnormal testis hormone production may suffice to give rise to a normal phosphatase concentration (see page 163).

— According to previous investigators (page 182), the chorionic gonadotropin exerts its effect on the prostate only via the testes.

— Judging by the phosphatase concentration, the dosage of chorionic gonadotropin administered is a maximum stimulation of the testes (see page 182).

Course during Treatment (characterized by the numbers 1, 2, and 3).

Course 1 shows with a great probability that the testes have not been stimulated, as prostatitis (se page 45) can be left

Figure 23.

Diagram showing 7 different Forms of the Course of the Concentration of Phosphatase during Treatment with Chorionic Gonadotropin in Cases with no Production of Phosphatase before the Treatment.

Ordinate: Concentration of phosphatase in K.P.U.
Heavily inked line along the abscissa: period of treatment.
y - 5 K.P.U. states lower limit of the concentration of phosphatase of normal, middle-aged men.

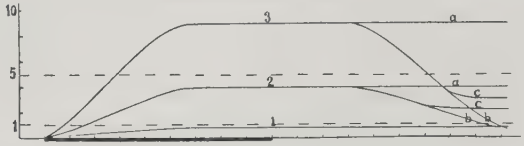


Table XXV

Distribution of the previously untreated Patients with initial Lack of Concentration of Phosphatase after Response to first Series of Treatment with Chorionic Gonadotropin.

(cf. the first twenty (except No. 98) in Table XXIV).

Reaction type after fig. 23	Description of reaction type (see page 187)	Numbers of patients	
		Adiposogenital dystrophy	Infantilism
1	no effect	174	170
2	subtotal imitation, or subtotal, provoked puberty		123
2 a	subtotal, provoked puberty	35 - 70 - 119	
2 b	subtotal imitation		49 - 54 - 79 - 126 149 - 194 - 196
2 c	subtotal, provoked puberty + subtotal imitation	193	97 - 191
3 a	total, provoked puberty	136	192
3 c	subtotal, provoked puberty + total imitation	68	

out of consideration in these patients, and probably also irreversible involution of the prostate.

Course 2 and Course 3 signify that the testes have responded to treatment with a production of hormone. It is not feasible to estimate whether the testes have responded with a normal production of hormone (i. e. normal for a middle-aged man). It may, however, justly be concluded that the testes have responded subnormally to the stimulation if testosterone treatment of the same patient has produced a higher phosphatase concentration than did the treatment with chorionic gonadotropin.

The subsequent course (characterized by the letters *a*, *b*, and *c*).

Course *a* may be due to the following: —

(I) Spontaneous puberty may incidentally have occurred during the treatment.

(II) The treatment with chorionic gonadotropin has, directly or through the influence on the gonads, improved the production of gonadotropin by the pituitary to such a degree that the production of testis hormone that has been started can be kept up.

(III) The previously inactive testes have been enabled through the vigorous stimulation to respond to the gonadotropin production of the pituitary, the intensity of which has not increased either during or after the treatment.

re (I). This possibility may be rejected because of the observation illustrated by Fig. 22 that spontaneous puberty causes a much slower increase of the phosphatase concentration than does provoked puberty. If Course *a* were an interfering spontaneous puberty, a slower increase of the phosphatase concentration would be expected during this course than during Course *b* and Course *c*, but such a difference does not exist.

re (II). It may be objected against this explanation that there is nothing to support the assumption that chorionic gonadotropin after discontinuance of the treatment should directly increase the faculty of the pituitary to produce gonadotropin, not to be mistaken for the activity of the pituitary during treatment, which probably decreases (Leonardt 1933). The alternative that it takes place via an influence on the gonads will be inconsistent with the observation that an increased supply of testosterone propionate to eunuchoids reduces an existing hypergonadotro-

pinuria. In what way a pituitary with subnormal function is influenced be testosterone, is not known however.

re (III). It is a reasonable, though hypothetic, assumption that a higher output of gonadotropin from the pituitary is required to cause infantile testes to function with regard to production of testis hormone than to retain a hormone production from the testes, which somehow or other have been enabled to function. Considering this, which is supported by Hamburger and Halvorsen's demonstration (1942) of sporadic hypergonadotropinuria in the years of puberty, the following hypothesis may be formulated: The production of gonadotropin by the pituitary in many hypandrogenic individuals is not sufficient to give rise to a production of testis hormone, but great enough to maintain it, a property which treatment with chorionic gonadotropin is able to make manifest.

Course *b* signifies that the testis reaction ceases when the treatment is discontinued. The cause may be that the production of gonadotropin by the pituitary is too low to retain a testis hormone production started from without, or it may be that the testes are so inactive that they can only respond to the large doses administered, but not to the normal or, possibly, increased production of the pituitary.

Course *c* signifies either that the pituitary does not produce sufficient hormone to keep up a normal production of testis hormone or — if the production of gonadotropin by the pituitary is normal or supranormal — that the testes even after the treatment require a stimulation stronger than the normal to enable them to function with normal intensity.

REVIEW OF THE SERIES

Among 19 previously untreated patients with primarily absent production of phosphatase, who were followed with phosphatase determinations during the first chorionic gonadotropin series (the first 20 patients in Table XXIV with the exception of No. 98) the possibilities mentioned above were realized to the extent shown in Table XXV.

The most frequent reaction is found to be Course 2, i. e. an increase of the phosphatase concentration to values somewhat below or about the lower limit of the normal (5 K.P.U.), where-

as lacking reaction (1) or a fully normal phosphatase concenduction of phosphatase (3 b) was not observed, whereas cessation after a subnormal phosphatase cencentration had been established (2 b), was a very frequent finding.

The Difference in the Phosphatase Reaction between the Infantilism Group and the Patients suffering from Adiposogenital Dystrophy.

In Table XXV the patients with infantilism and adiposogenital dystrophy are grouped according to their manner of reaction to the first chorionic gonadotropin course.

The table shows for the same two groups of patients the conditions of the production of phosphatase after the treatment with chorionic gonadotropin had been discontinued. From the table it is seen that all the patients with adiposogenital dystrophy retain the production of phosphatase after treatment has been discontinued, whereas the patients of the infantilism group with three exceptions display cessation of the production of phosphatase commenced during the treatment. As is further shown by Table XXVI, this difference is not due to the first-named patients being older, it is indeed possible that chorionic gonadotropin may provoke puberty, when the patient has reached a certain age (about or in the years of puberty), and that this effect fails to appear in the patients of the infantilism group, because they are over that age.

Nor is the difference due to any larger size of the testes of the patients suffering from adiposogenital dystrophy, so that they might therefore be more inclined to pass into puberty, or to the administration of larger quantities of chorionic gonadotropin to these patients than to others, — and, finally, they have not even been under observation for a shorter period so that a possible decrease would not have had time to manifest itself.

The fact that provoked puberty is chiefly met with in patients suffering from adiposogenital dystrophy according to what was mentioned on page 190, may be explained by a higher output of gonadotropin by the pituitary in these patients than in the infantilism group, even so much higher that it is able to keep up a production of testis hormone started from without, though at the moment of examination not sufficient to start it itself.

However, the output of gonadotropin is not always able to

Table XXVI

Six Patients suffering from Adiposogenital Dystrophy and 10 of the Group of Infantilism — all previously untreated — distributed partly according to Phosphatase Reaction after Discontinuance of first Treatment with Chorionic Gonadotropin, partly according to Duration of Latent Period, Concentration of Phosphatase during Treatment, total Dose of Chorionic Gonadotropin, Duration of Observation after Treatment, Ages of the Patients, and Volumes of their Testes.

	Adiposogenital Dystrophy		Infantilism	
	Prodnction of phosphatase after discontinuance of treatment compared with the initial production (see Fig. 23 and Table XXV)			
	status quo ante acta	improved production	status quo ante acta	improved production
	2b 3(b)	2a,c 3a,c	2b 3(b)	2a,c 3a,c
Latent period in months		Number of patients		
about 1	—	3	2	2
1 to 2	—	2	2	1
2 to 3	—	—	3	—
not determined		(1)		
Concentration of phosphatase in K. P. U. during treatment				
about 1	—	—	1	—
1 - < 5	—	1	4	—
about 5	—	3	2	2
≥ 5	—	2	—	1
Total dose of chorionic gonadotropin in 1000 I. U.				
< 30	—	—	1	—
30 to < 40	—	2	1	—
40 to < 50	—	3	4	3
≥ 50	—	1	1	—
Observation after treatment, stated in months				
1 to < 2	—	1	2	2
2 to < 4	—	1	3	1
4 to < 6	—	1	—	—
≥ 6	—	3	2	—
Ages of patients				
< 12	—	1	—	—
12 to < 14	—	4	1	—
14 to < 16	—	—	—	2
16 to < 18	—	1	3	1
≥ 18	—	—	3	—
Volume of testes in ml				
< 2	—	2	3	—
2 to < 10	—	3	3	3
≥ 10	—	—	—	—
not determined		(1)	(1)	
Total:	0	6	7	3

keep up the production of testis hormone to the same extent as during the treatment; the production of phosphatase in patients 68 and 193 thus remained at a lower level than during the treatment. The remaining four patients present a hypophyseal reac-

tion (continuation of the attained testis hormone production) which could not have been better in normal boys. Thus the assumption of a missing production of gonadotropin by the pituitary in these four patients is not supported by these experiments.

Another important observation, which appears from Tables XXIV and XXV, will be discussed in detail, namely, that most of the patients in the first chorionic gonadotropin course obtained a phosphatase concentration of about 5 K. P. U. only, or less; in other words, the production of phosphatase is far from always becoming normal in the first chorionic gonadotropin course. A deficient production of gonadotropin by the pituitary cannot be made responsible for this, however, for the treatment with chorionic gonadotropin alone with the doses administered must be supposed greatly to exceed what a normal pituitary can yield (cf. page 180). Moreover, it has been shown (see page 182) that an increase of the dose of chorionic gonadotropin above 1500 I.U. administered 3 times a week generally is without further influence on the phosphatase concentration. The dosage employed therefore represents a maximum gonadotropin stimulation, irrespective of the possible contribution of the pituitary.

There are then three possibilities left: Either that the producduction of testis hormone despite the maximum stimulation of the testes, cannot be increased to normal height, or that the production of testis hormone does become maximal, but that the prostate is too little developed to respond with a maximum production of phosphatase to its adequate stimulus, the testis hormone, or, finally, that besides the maximum production of testis hormone the prostate requires the presence of other hormones for the full production of phosphatase.

The two last-mentioned possibilities have been elucidated by the experiments with testosterone treatment (see page 87 and Fig. 1).

As the influence of chorionic gonadotropin on the production of phosphatase in normal boys in prepuberty and puberty has not been investigated in this work, the question whether the frequently subnormal phosphatase reaction to a maximum chorionic gonadotropin influence is really a sign of abnormally poor function of the testes, or whether it is physiological for just this stage of development, must be left open for the present. At any rate the possible affection of the testes in patients

suffering from adiposogenital dystrophy has been so slight that the improvement obtained with a single course of chorionic gonadotropin persists.

After all, this condition with a subnormal production of phosphatase, as a rule, does not continue. Table XX shows that reexamined individuals, who had previously been treated for adiposogenital dystrophy and who are now clinically cured, though constantly somewhat adipose, nearly all had higly normal values for the phosphatase concentration. Thus a rise must take place later. Such rises have actually been observed in the present series of patients, and they may occur long after discontinuance of the treatment, as shown on page 198.

These findings must mean either that the prostate has become able to respond to the production of testis hormone with a fully normal production of phosphatase or that the output of testis hormone has increased spontaneously or, finally, that the production of another — hypothetical — hormone stimulating the prostate has come into play. The fact that the virilization often does not progress until the moment when the phosphatase concentration rises spontaneously, goes against the supposition that it is just the prostate that has become more sensitive, and speaks in favour of the androgen production actually having increased essentially, and this means that the provoked puberty here has been followed by spontaneous puberty.

If puberty — such as it manifests itself by the production of phosphatase after having been started by one chorionic gonadotropin series — is able to follow a normal course, it is natural to assume that it is also able to occur spontaneously and to be completed without these patients receiving treatment. Such a conception actually prevails in the literature (see page 137). The present series includes one untreated patient with adiposogenital dystrophy, which was diagnosed in the 7th year of his life (No. 173); on examination at the age of 14½ years he was found to have more abundant pubes, though without any growth of hair along the linea alba, moreover hirci, but no growth of beard, thus presenting advanced, not retarded puberty. Accordingly, the phosphatase concentration was 13.4 K. P. U.. The patient was still obese.

According to the literature on the subject there is every reason to assume that treatment with c h o r i o n i c g o n a d o-

tropin in adiposogenital dystrophy is superfluous in many cases, because the obesity frequently remains uninfluenced by the treatment, and puberty in most cases will occur spontaneously and be completed. If puberty has not begun before the 16th year, it will be indicated, as was stressed by S. C. Werner (1941) and several others, to commence a treatment with gonadotropin. From the preceding it is evident that chorionic gonadotropin in the dosage administered even early in prepuberty is able to start a process of sexual maturation which is not maximal, but which may later be increased spontaneously. For that purpose a single course of about 45,000 I. U. is sufficient.

In case of retentio testis, this may be an indication for treatment with chorionic gonadotropin in prepuberty.

The Phosphatase Production in repeated Courses of Chorionic Gonadotropin Injections.

The question now arises whether the difference between patients, who do not respond with a lasting production on phosphatase to the courses, and those in whom production, once started, continues, is of qualitative or quantitative character, in the latter case so that, merely by means of larger or more doses, puberty can be provoked in those patients who have responded with imitation of puberty to the first courses.

To elucidate this question, several patients were subjected to repeated courses of treatment. In the present work such a form of treatment was preferred to continuous treatment, because it becomes possible not only to follow changes in the intensity of the reaction (the level attained) but also changes in the latent period and, further, to decide more accurately the quantity of chorionic gonadotropin required to bring about a lasting production of phosphatase.

A. Imitation of Puberty after the first Course.

All the seven patients — all of the infantilism group — who according to Table XXIV after the first course showed arrest of the production of phosphatase were subjected to the next course of treatment. The phosphatase reactions are shown in Fig. 24.

The latent period during the second course is distinctly shorter than during the first course.

The influence on the phosphatase level is strikingly better in three patients (Nos. 49, 54, and 149) and weaker in one patient (No. 126) than the effect of the first course. Nos. 194 and 196 were controlled insufficiently in the second course. In No. 79 the effect is alike in the two courses of treatment, but the subsequent intensive treatment increases the phosphatase concentration to the normal. After the second course of chorionic gonadotropin No. 49 was treated with equine gonadotropin (Antex Leo), which, however, did not increase the level any further. This patient was subsequently treated with testosterone propionate in doses of 25 mg 3 times a week, 30 intramuscular injections altogether. This treatment for the first time increased the phosphatase concentration to doubtlessly normal values, which shows that the prostate is able to respond with a higher production of phosphatase than the one observed during the treatment with chorionic gonadotropin. Thus this patient's testes must be responsible for the defective production of phosphatase during the treatment with chorionic gonadotropin. A subsequent final course of treatment with chorionic gonadotropin (combined with thyroid treatment) increased the phosphatase concentration still more (about 20 K. P. U.); a reliable explanation of this rise cannot be given. May be the preceding testosterone treatment — or the simultaneous thyroid treatment — has improved the reactivity of the testes to chorionic gonadotropin; it cannot be excluded either that the testosterone treatment has enabled the prostate to respond more vigorously to the testis hormone production of the organism. This is suggested by the fact that the phosphatase level reached during the testosterone treatment persists after the discontinuance of the treatment. As was shown on page 95, thyroid treatment alone does not influence the production of phosphatase but possibly an augmentation effect of the combined thyroid and chorionic gonadotropin treatment comes into play (cf. Hellbaum, 1936).

Control of the development after the second course shows that only two of the seven patients (Nos. 49 and 194) have experienced persistently improved production of phosphatase (provoked puberty) whilst the output of testis hormone in the remaining five patients stopped again.

Three of these patients (Nos. 54, 79, and 149) were subjected to a third course of treatment which, in No. 149, was very intensive and brought a lasting, though very faint production of phosphatase; in the other two patients the output of testis hormone after the treatment stopped for the third time.

Lastly, patient No. 170 may be mentioned; during the first course he obtained a production of secretion whereas the production of phosphatase was not considerable. The subsequent very intensive treatment gave rise to a somewhat more considerable production of phosphatase which did not continue, however.

B. Provoked Puberty after the first Course.

In 9 (Nos. 35, 68, 70, 97, 119, 136, 191, 192, and 193) of the patients listed in Table XXIV, who prior to treatment lacked production of phosphatase, the subsequent course showed that the first course of treatment hat brought about a permanent production of phosphatase which, however, in some of the cases (e. g. 68 and 97, see below) adjusted itself at a lower level than during the treatment.

Only two out of these 9 patients (Nos. 68 and 97) were submitted to another course of treatment. The phosphatase concentration of No. 68 then rose to the same normal level as during the first course, decreasing so low as after the first. The reaction of patient No. 97, was about the same.

Conclusion.

There is a certain possibility of provoked puberty occurring in very hypandrogenic patients of the infantilism group after repeated treatment with chorionic gonadotropin, even though the first course has given rise to imitation of puberty, but it is very little probable that such a change in the response of testes will occur.

If the first course of treatment has brought about subtotal provoked puberty, continued treatment will not always lead to an appreciable increase of the intensity of the underlying production of testis hormone.

Spontaneous Puberty after concluded Chorionic Gonadotropin Treatment.

Long after the termination of the treatment the phosphatase concentration may remain at the same level. In seven of the patients listed in Table XXIV (Nos. 35, 63, 68, 70, 97, 134, and 136), however, a rise in the phosphatase concentration was observed, which led to a constantly increased production of phosphatase (see Fig 24). This increase set in several months after the treatment had been discontinued, and it can therefore be considered out of the question that chorionic gonadotropin has caused it directly.

It does not seem to be a question of an improved reaction of the prostate to an unchanged influence of testis hormone, since the development of the remaining somatic sex characters is accelerated after the occurrence of the rise. Thus it seems that a puberty process is underlying the rise which, therefore, will be termed s p o n t a n e o u s p u b e r t y in the following.

Before the beginning of treatment 2 out of the 7 patients (Nos. 63 and 134) presented a certain subnormal production of phosphatase. In these two patients the spontaneous increase, which was observed later, probably has to be regarded as an intensification of the same process which had already commenced before the treatment.

On the basis of this series it cannot be said with certainty that the improvement of the sex character brought about by the treatments promotes the appearance of the mentioned „spontaneous" puberties or not. If it does not, the result attained in these patients with the courses of treatment is nothing but an anticipation of a development which would have taken place at any rate.

Combinations of Imitation of Puberty, provoked Puberty and spontaneous Puberty in the same Individual. Previously untreated and previously treated Patients.

Fig. 24 shows all the previously untreated or treated hypandrogenic patients who have been followed through one or several courses of treatment with chorionic gonadotropin and whose phosphatase concentration prior to the first of these courses was below 5 K. P. U.; in Table XXVII the patients are grouped according to the course of their puberty.

Table XXVIII moreover shows the number of patients who have attained the various types of puberty. It appears from the table that half of the patients of the infantilism group attained no puberty but merely imitation of puberty. On the other hand, all the patients suffering from adiposogenital dystrophy attained puberty; one patient (No. 151), however, responded slightly to the first course but attained puberty during the next course.

Both among these patients and those of the infantilism group spontaneous puberty occurred in about two-thirds of the cases, in which puberty is present. Total or subtotal puberty was attained to much about the same extent in the two groups of patients.

The Concurrence of Imitation and Puberty.

Among the fifteen patients of the infantilism group, in whom the first course, which was followed with analyses, caused imitation, about one-third (i. e. six) later attained provoked or spontaneous puberty. Six out of the remaining 9 patients, in whom imitation of puberty only was observed, were more than 20 years old, therefore they will scarcely ever arrive at spontaneous puberty. Only one of the 6 patients, in whom puberty has replaced an imitation, was more than 19 years old when puberty ensued.

The Concurrence of Provoked and Spontaneous Puberty.

In 10 of the patients subtotal provoked puberty was observed at a certain moment. "The rest of the puberty" of these patients must thus still be to come. In continued observations by means of phosphatase analyses it was found that this was effected entirely in three of the six patients suffering from adiposogenital dystrophy and in one of the four patients of the infantilism group, whereas in the remaining six patients it had not yet occurred at the end of the observation; among these six there are three patients of the first group between 12 and 14 years old, whereas the three patients of the infantilism group are between 14 and 17 years old (Table XXVIII).

The result of treatment in the four patients, who subsequently attained spontaneous puberty, is probably just an anticipation

of part of the puberty which nevertheless will ensue spontaneously later.

Summarizing, it may be said that imitation of puberty is seldom met with in the treatment of patients suffering from adiposogenital dystrophy in the years of puberty, that an imitation (which is mostly seen in the infantilism group) fairly seldom is followed by provoked or spontaneous puberty, and, finally, that a provoked puberty often will change into spontaneous puberty.

Figure 24.

Concentration of Phosphatase and other Properties i 36 hypandroid Patients observed during a prolonged Period.

The Figure comprises the following Patients: Nos. 7, 8, 12, 35, 36, 41, 42, 49, 54, 55, 59, 63, 66, 68, 70, 74, 79, 97, 119, 123, 126, 128, 134, 136, 149, 151, 153, 164, 165, 170, 189, 191, 192, 193, 194 and 196 arranged according to serial number.

Ordinate: Concentration of phosphatase in K.P.U.

See also explanation in text, page 81.

The table accompanying the curves shows:

— The age of the patient as shown by the following examples:
14.9 = 14 years and 9 months,
15.11 = 15 years and months.

— The total dose in a series of treatment stated in:
1000 I. U. for Physex (Chorionic gonadotropin), Antex (Equine gonadotropin), 1000 I. B. U. for Ovex (Oestradiol monobenzoate), and in grammes for testosterone propionate and methyl testosterone.

— The daily dose stated in T. U. for tablettae glandulae thyreoideae.

— The level of the concentration of phosphatase stated as follows:

"0"	
<1	K. P. U.
about 1	—
1-5	—
about 5	—
5-10	—
etc.	

— The type of sexual maturation estimated from the phosphatase reaction during and after each series of Physex.

— The development of the other sex characters described as stated on page 72.

— Retention of the right or the left testis termed d, respectively s.

— Height in cm, Weight in kg.

Figure 24. (continued)

Patient No. 7. **Eunuchoidismus.**

Year and month	1944.6-1944.12		1945.5-1945.6		1946.3 -1946.6		1946.9-1949.10		1946.11
Age	32.1	32.7	33.0	33.1	33.10	34.1	34.4	34.5	34.6
Physex	49.5		15.0		33.0				
Oestradiol monobenzoate							100		
Concentration of phosphatase*)			<1	1-5	<1	1-5	1-5	1-5	1-5
Type of sexual maturation			Imitation subtotal		Provoked puberty subtotal				
Volume of testes					about 1			about 1	
Diameter of penis					19			29	
Length of penis					41			50	
Pubes	2				2				
Terminal growth of hair	2				2				
Height					180			180	
Height when sitting					80			80	
Weight					70			77	

*) Expressed secretions contain admixtures of urine.

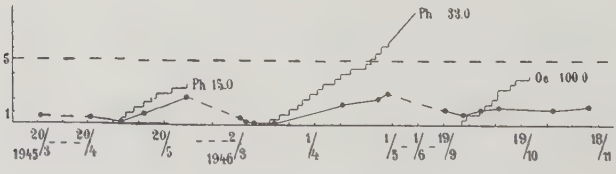


Figure 24. (contiuned)

Patient No. 8. **Infantilismus primarius.**

r and month	1944.10-1945.2		1945.3 -1945.3		1945.4 -1945.5		1945.6-1945.6		1945.7	1947.4
	16.5	16.9	16.10	16.10	16.11	17.0	17.1	17.1	17.2	18.11
sex	34.5		1				2			
ex					4.95					
centration hosphatase			about 1	1-5	1-5	about 1	<1	>5	1-5	10-20
e of sexual uration			Imitation subtotal				Imitation total			spontaneous puberty total
ume of testes			5.4							19.3
meter of penis			22							22
gth of penis			35							70
es	0		3							6
minal growth air	0		1							4
ght	147		150							162
ght when ng	65									75
ght	44		49							57

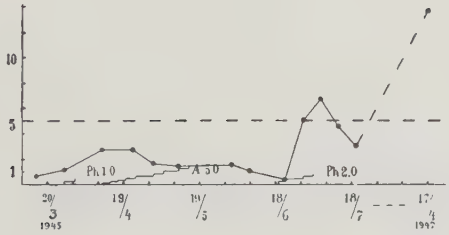


Figure 24. (continued)

Patient No. 12. **Pubertas tarda.**

Year and month	1944.11-1945.4		1945.11-1946.2		1947.1
Age	31.0	31.5	32.0	32.3	33.2
Physex	85.5		46.5		
Concentration of phosphatase	10-20		about 5	10-20	1-5
Type of sexual maturation	spontaneous? provoked? Puberty subtotal + Imitation total		Imitation total		
Volume of testes			3.4	10.2	5.0
Diameter of penis			25	28	25
Length of penis			53	54	61
Pubes	3	4	4	6	5
Terminal growth of hair	2	3	3	4	3
Height	169			170	
Height when sitting	80			83	
Weight	74			80	

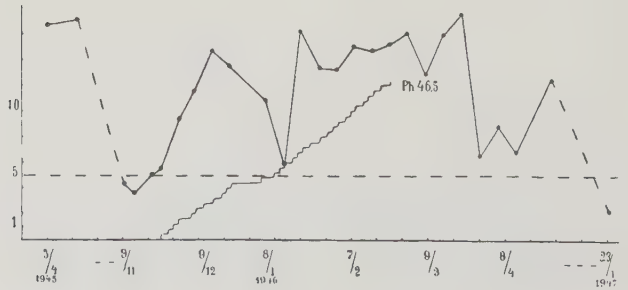
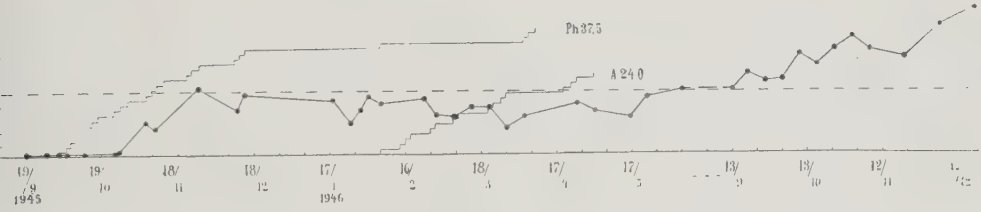


Figure 24. (continued)

Patient No. 35. **Dystrofia adiposo-genitalis.**

Year and month	1945.10	1945.12	1946.2	1946.5	1946.9	1947.4
Age	16.7	16.9	16.11	17.2	17.6	18.1
Physex	31.5		6.0			
Antex			24.0			
Concentration of phosphatase	<1	1-5	1-5	1-5	about 5	10-20
Type of sexual maturation	provoked puberty subtotal				spontaneous puberty total	
Volume of testes	about 3				5.8	13.2
Diameter of penis	16				24	26
Length of penis	20				50	71
Pubes	2				3	4
Terminal growth of hair	2				3	3
Height	165					175
Height when sitting	78					78
Weight	75					83



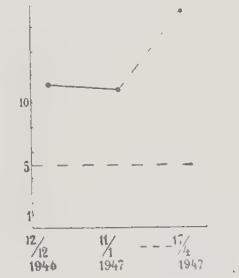
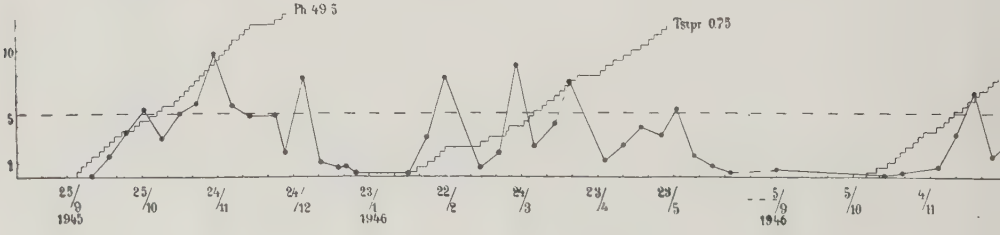


Figure 24. (continued)

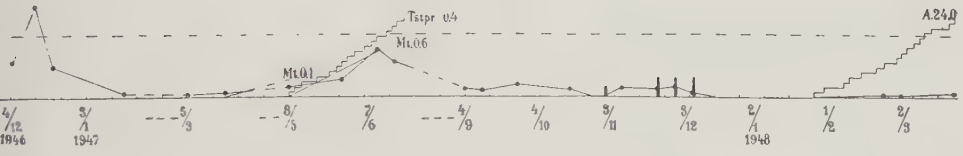
Patient No. 36. **Infantilismus secundarius.**

Year and month	1945.9-1945.12		1946.2 -1946.5		1946.10-1946.11	
Year of life	21.5	21.8	21.10	22.1	22.6	22.7
Physex	49.5				10.0	
Antex						
Testosterone propionate			0.75			
Methyl testosterone						
Concentration of phosphatase	"0" about 5		<1 about 5		<1 about 5	
Type of sexual maturation	Imitation subtotal				Imitation subtotal	
Volume of testes	<2.4	2.4		2.5	d + 0.6	
Diameter of penis	19			22	25	
Length of penis	50			82	80	
Pubes	2				3	
Terminal growth of hair	1				1	
Height		147		148	148	
Height when sitting		72		71	72	
Weight		48		49	46	



*) Testosterone propionate crystallicum Ciba. 50 + 100 + 100 + 100 mg subcutaneously.

1947.3 -1947.5		1947.5-1947.6	1947.10-1947.12		1948.1-1948.3		1948.10-1949.1	
22.11	23.1	23.2	23.6	23.8	23.9	23.11	24.6	24.9
					24.0		78.0	
	0.4		0.35*)					
0.1	0.63							
<1	about 1	1-5	<1	<1	<1	<1	<1	<1
2.8					1-2			
					24			
					71			
4					4			
1					1			
147		147				148	148	
72		73				73	74	
47		49				48	49	



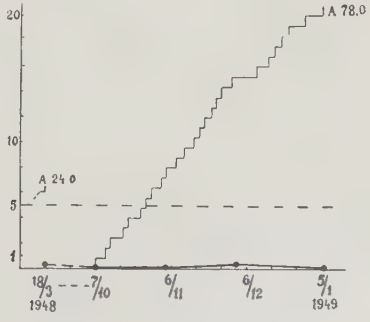
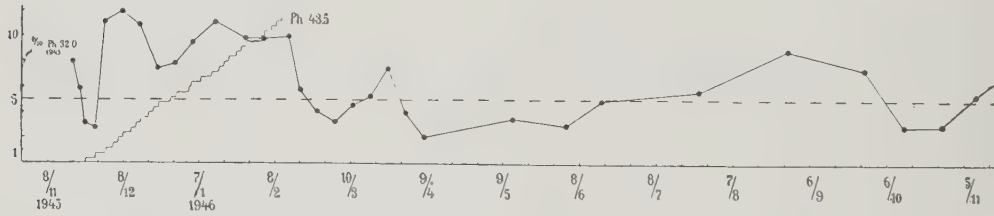


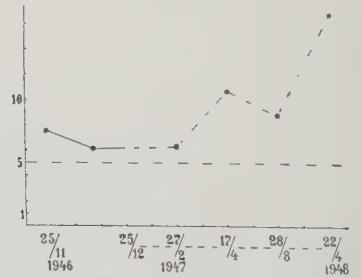
Figure 24. (continued)

Patient No. 41. **Infantilismus primarius.**

Year and month	1945.7-1945.10		1945.11-1946.2		1947.4	1947.8	1948.4
Age	15.0	15.3	15.4	15.7	16.9	17.1	17.9
Physex	32		43.5				
Concentration of phosphatase		>5	1-5 about 10		about 5*) about 10*)	10-20	10-20
Type of sexual maturation	spontaneous? provoked? Puberty subtotal + imitation total		Imitation total				spontaneous puberty total
Volume of testes			3.3	6.2	11.2	11.1	13.8
Diameter of penis			16		28	24	25
Length of penis			50		63	77	87
Pubes	2	3	3	3	3	5	4
Terminal growth of hair	1	1	1	1	3	3	3
Height	145	148	150		158	160	164
Height when sitting	72	72			76	76	81
Weight	35	38	38		45	45	49

*) Values with intervening gaps.



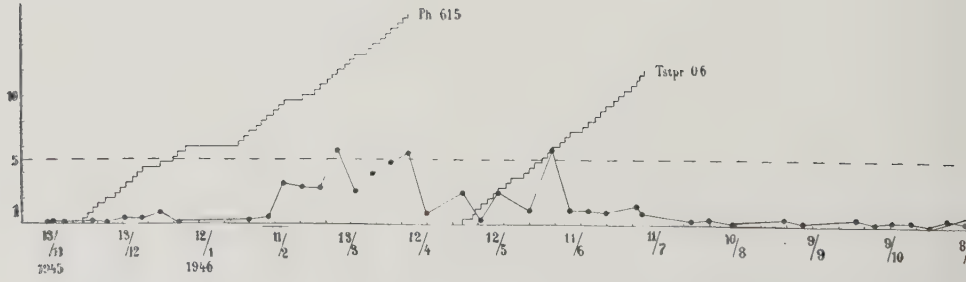


Patient No. 42
See next page.

Figure 24. (continued).

Patient No. 42. **Infantilismus secundarius.**

Year and month	1943.9-1945.3		1945.11-1946.1		1946.2-1946.4		1946.5-1946.7	
Age	18.	20.3	20.11	21.1	21.2	21.4	21.6	21.7
Physex	48.5		22.5		39.0			
Testosterone propionate							0.6	
Methyl testosterone								
Thyroid extract								
Concentration of phosphatase*)			<1 about 1		<1 about 5		1-5 about 5	
Type of sexual maturation			Imitation subtotal					
Volume of testes			1.6		3.8		2.3	
Diameter of penis			15				28	
Length of penis			42				62	
Pubes	0	2	2		3		3	
Terminal growth of hair	0	1	1		1		1	
Height			162					
Height when sitting			75					
Weight			60					



1946.10	1947.1	1947.3	1947.5	1947.10	1948.1	1948.6
21.10	22.1	22.3	22.5	22.10	23.1	23.6

3.18

0.64 0.82 3.18 2.0

200-400

<1 <1 about1 <1 about5 about1 <1

		3.8	2.4
		24	26
		56	75
	3	3	6
	1	1	2
164	165	165	
77	77	78	
64	59	69	

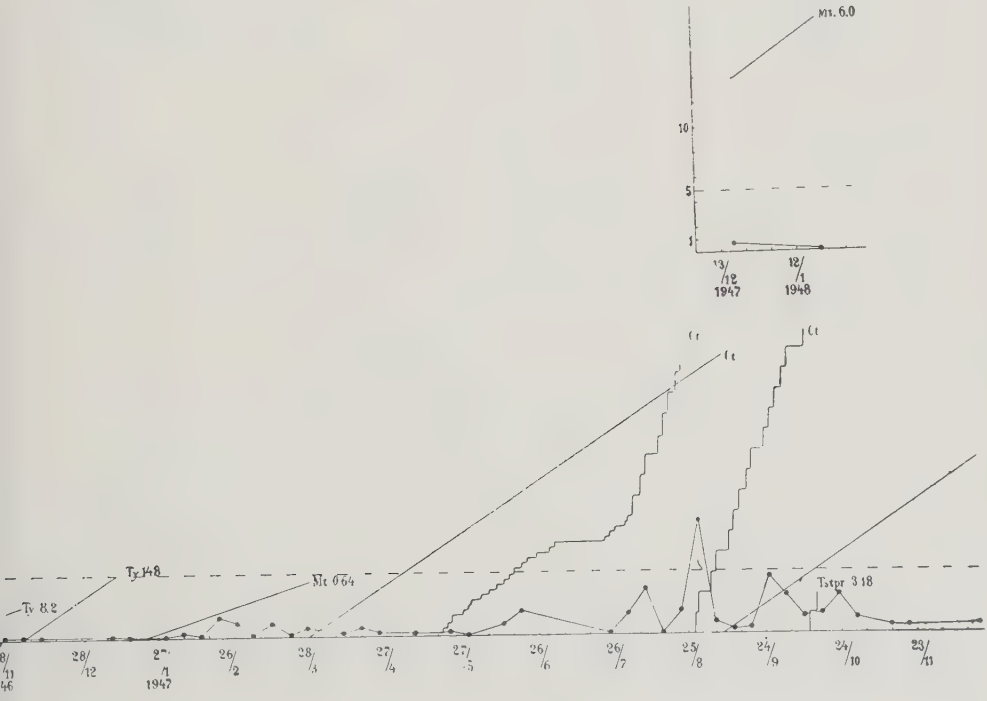
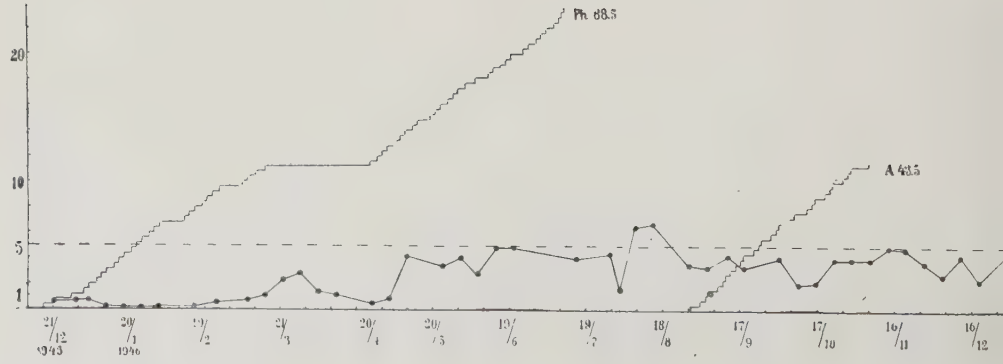


Figure 24. (continued)

Patient No. 49 **Infantilimus primarius.**

Year and month	1945.12-1946.3		1946.4-1946.7		1946.8-1946-11	
Age	16.9	17.0	17.1	17.4	17.5	17.8
Physex	42		46.5			
Antex					43.5	
Testosterone propionate						
Thyroid extract						
Concentration of phosphatase	"0"	1-5	<1	1-5	1-5	1-5
Type of sexual maturation	Imitation subtotal		provoked puberty subtotal			
Volume of testes	about 2	2.8		5.1	3.7	3.4
Diameter of penis		23		24	24	24
Length of penis		50		70	70	62
Pubes	0	2		3	3	3
Terminal growth of hair	0	1		1	1	1
Height	144	148	151	151	152	153
Height when sitting	70	72		74	75	75
Weight	32	40		49	45	46



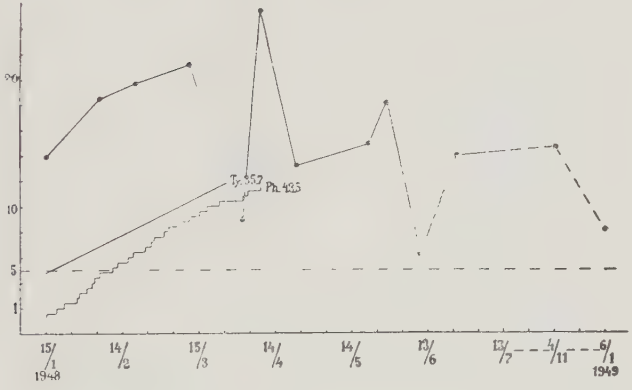
1947.1	-1947.3	1947.8	1948.1	-1948.4	1948.11	1949.1
17.10	18.0	18.5	18.10	19.1	19.8	19.10

43.5

0.75

200-300

1-5	5-10	5-10	about10 provoked puberty	about 20 total	10-20	
			7.6	9.8	7.9	10.2
			25	28		23
			75	89		79
3	3		3	3	3	3
1	1		1	1	1	1
153	154	155	156	157	159	159
74	74	76	77	78	79	79
46	49	45	50	55	54	52



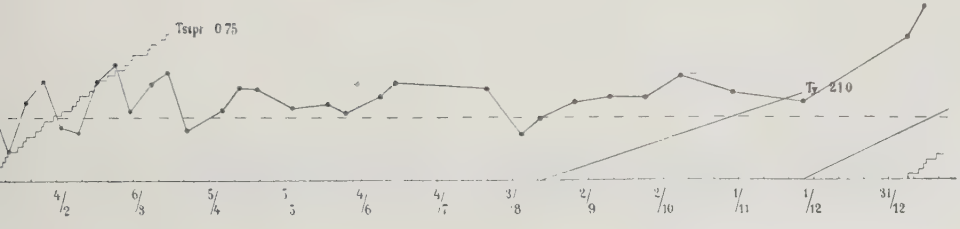
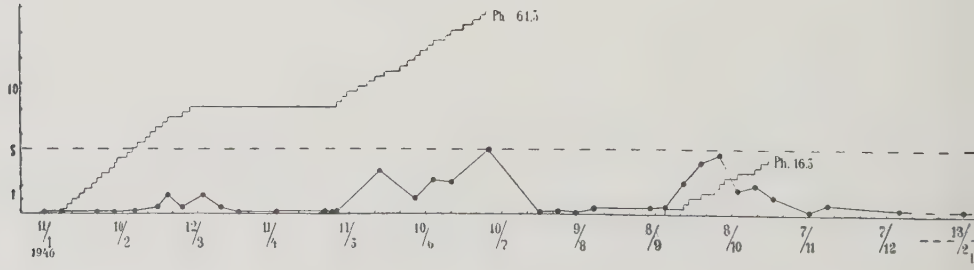


Figure 24. (continued)

Patient No. 54. **Infantilismus primarius.**

Year and month	1946.1-1946.3		1946.5-1946.7		1946.9-1946.10	
Age	16.1	16.3	16.5	16.7	16.9	16.10
Physex	31.5		30		16.5	
Concentration of phosphatase	<1	about1	<1	1-5	<1	1-5
Type of sexual maturation	Imitation subtotal		Imitation subtotal		Imitation subtotal	
Volume of testes	2.9	5.5	2.9		5.3	
Diameter of penis		25	22		24	
Length of penis		57	61		82	
Pubes	1	2	3		5	
Terminal growth of hair	0	1	1		1	
Height	149	149	151		154	
Height when sitting	71	71	72		73	
Weight	40	44	44		46	



1947.7	1947.10-1948.4	
17.7	17.10	18.4
	142.5	
<1	<1 about 1	
	Imitation subtotal	
12.0		10.8
30		
95		
5	5	6
2	2	3
159		162
76		79
48		58

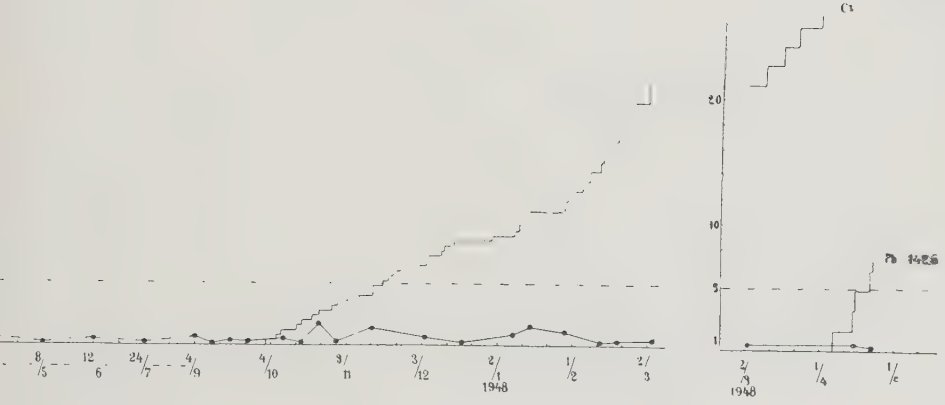


Figure 24. (continued)

Patient No. 55. **Infantilismus secundarius.**

Year and month	1945.10-1945.11		1946.1-1946.2		1946.3 -1946.6		1946.7	1947.4	1948.3	1948
Age	16.5	16.6	16.8	16.9	16.10	17.1	17.2	17.11	18.10	19
Physex	18.0		24.0		45.0					
Antex	1.5									
Concentration of phosphatase*)			"0"	1-5	<1	1-5	about1*)	about 10	about 10	about
Type of sexual maturation			Imitation subtotal		Imitation subtotal			spontaneous puberty total		
Volume of testes				5.6	11.4	5.3		13.4		
Diameter of penis				22	20	24		23		
Length of penis				42	54	64		83		
Pubes			2	2	2	4		4		
Terminal growth of hair			1	1	1	1		2		
Height	150	150	150	153	153			160	161	
Height when sitting			69	69	70			75	76	
Weight			46	50	48			55	54	

*) Values with intervening gaps.

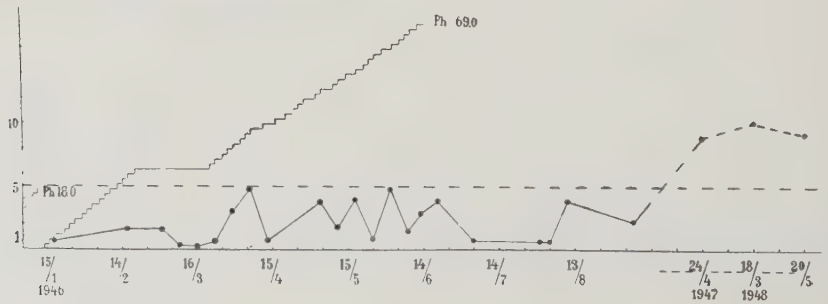


Figure 24. (continued)

Patient No. 59. **Dystrofia adiposo-genitalis.**

Year and month	1944.5-1944.9		1946.2-1946.3		1946.9	1947.4	1947.12
Age	12.9	13.2	14.6	14.7	15.1	15.8	16.4
Physex	30.0		13.5				
Concentration of phosphatase*)			1-5	<5	1-5		1-5
Type of sexual maturation	spontaneous? provoked? Puberty subtotal		Imitation total				
Volume of testes			17.0		17.9		
Diameter of penis	20		24		31		
Length of penis	50		74		74		
Pubes	2		6		6		
Terminal growth of hair			3		4		
Height			171			174	
Height when sitting			83			86	
Weight			72			75	

*) Values with intervening gaps.

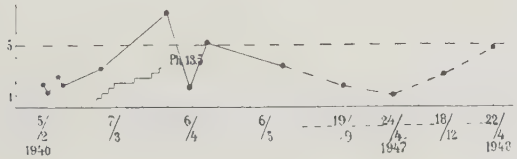


Figure 24. (continued)

Patient No. 63. **Dystrofia adiposo-genitalis.**

Year and month		1946.1-1946.6		1946.9	1947.5	1947.9
Age		12.8	13.1	13.4	14.0	14.4
Physex		50.0				
Concentration of phosphatase		1-5	1-5	about 5	10-20	about 20
Type of sexual maturation	spontaneous pnberty subtotal	?			spontaneous puberty total	
Volume of testes			1.5	5.6	11.1	11.4
Diameter of penis			25	23	26	28
Length of penis			58	76	81	94
Pubes		0	2	2	4	5
Terminal growth of hair		0	1	2	2	2
Height		152	156	159	165	168
Height when sitting		70			77	78
Weight		55	55	57	61	60

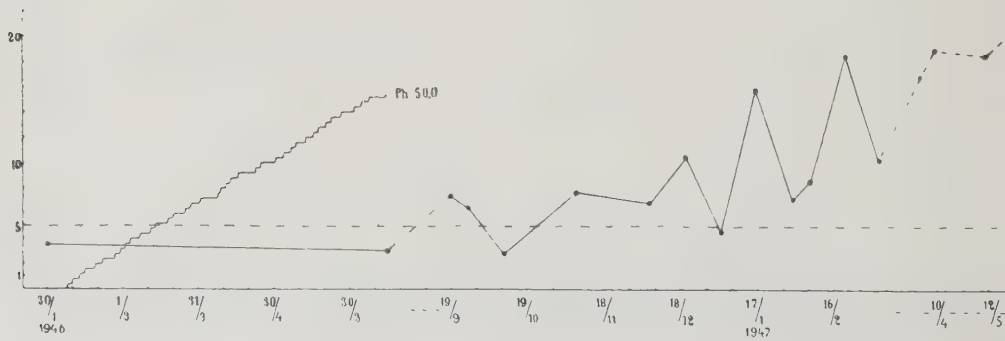
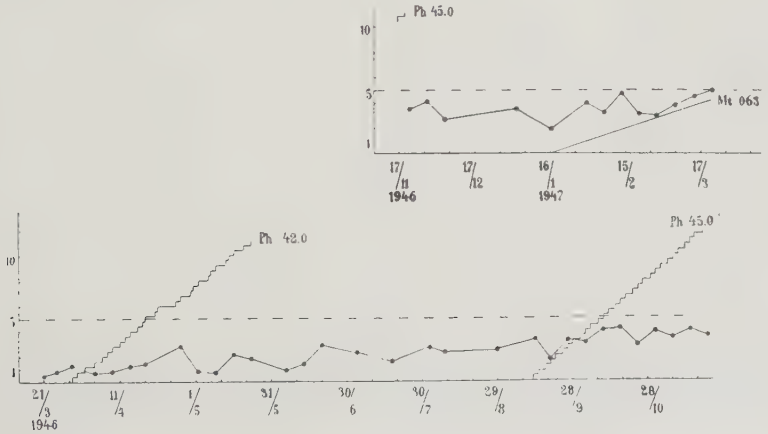


Figure No. 66. (continued)

Patient No, 66, **Dystrofia adiposo-genitalis.**

Year and month	1946.3-1946.5		1946.9-1946.11		1947.1 -1947.3	
Age	16.0	16.2	16.6	16.8	16.10	17.0
Physex	42.0		45.0			
Methyl testosterone					0.63	
Concentration of phosphatase	about1	1-5	1-5	1-5	1-5	about 5
Type of sexual maturation	spontaneous puberty subtotal	provoked puberty subtotal		Imitation subtotal		
Volume of testes	about1.5	1.9	1.2	2.1	about 2	
Diameter of penis	20	21	26	26		
Length of penis	33	62	54	72		
Pubes	2	2	2	2	3	
Terminal growth of hair	1	1	1	1	1	
Height	155	155	157	158	159	
Height when sitting	74	73	74	75	76	
Weight	59	50	53	57	57	



Fignre 24. (continued)

Patient No. 68. **Dystrofia adiposo-geniralis.**

Year and month	1946.1 -1946.3		1946.5-1946.7			1946.10	1947.5	1948.4
Age	12.10	13.0	13.2	13.4		13.7	14.2	13.1
Physex	43.5		19.5					
Concentration of phosphatase	"0"	about10	about 5	10-20	5-10	about 10	about 10	about 15
Type of sexual maturation	provoked puberty subtotal + imitation total		provoked puberty subtotal + imitation total					spontaneous puberty total
Volume of testes		4.6	4.9				11.2	19.8
Diameter of penis		25	25				26	34
Length of penis		46	50				68	95
Pubes		2	2				3	5
Terminal growth of hair		1	1				1	2
Height			160			164		175
Height when sitting			77			79		84
Weight			62			66		83

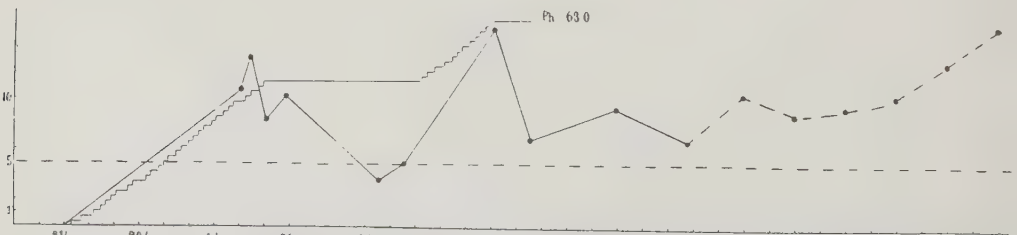


Figure 24. (continued)

Patient No. 70. **Dystrofia adiposo-genitalis.**

Year and month	1946.3-1946.6		1947.5	1947.9	1948.4
Age	13.8	13.11	14.10	15.2	15.9
Physex	45.0				
Concentration of phosphatase	"0"	1-5	1-5	5-10	>10
Type of sexual maturation	provoked puberty subtotal			spontaneous puberty total	
Volume of testes		2.2	9.4	13.5	13.3
Diameter of penis		24	26	28	32
Length of penis		49	74	91	84
Pubes	0	3	3	6	6
Terminal growth of hair	0	2	2	3	3
Height	148	152	160	162	166
Height when sitting	72	72	77	79	80
Weight	57	56	61	64	72

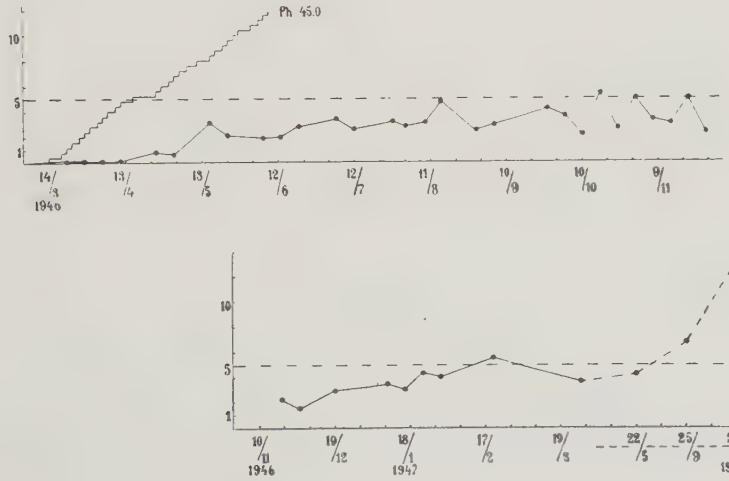
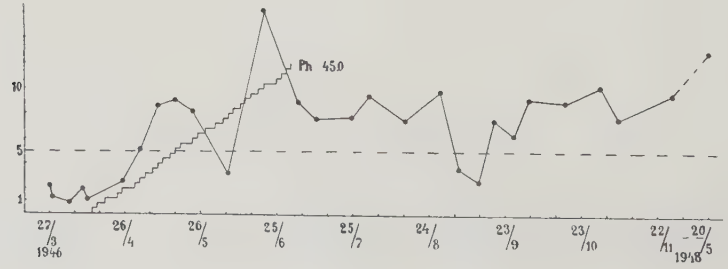


Figure 24. (continued)

Patient No. 74. **Infantilismus secundarius.**

Year and month	1946.3	1946.4-1946.7	1946.10	1948.5
Age	17.4	17.5 17.8	17.9	19.6
Physex		45.0		
Concentration of phosphatase		1-5 5-10	5-10	about 10
Type of sexual maturation	spontaneous puberty subtotal	provoked puberty total		
Volume of testes	11.9	11.0	16.2	27.3
Diameter of penis	24	29	28	31
Length of penis	68	86	94	99
Pubes	2	5	4	6
Terminal growth of hair	1	2	2	3
Height		150	153	160
Height when sitting		62	72	79
Weight		51	51	57

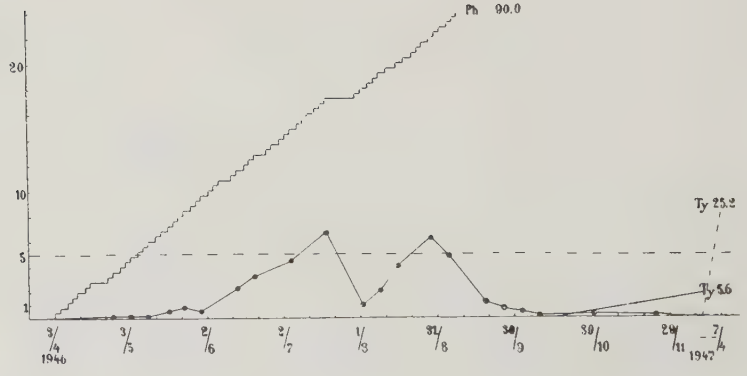


Patient No. 79
See next page.

Figure 24. (continued)

Patient No. 79. **Infantilismus secundarius.**

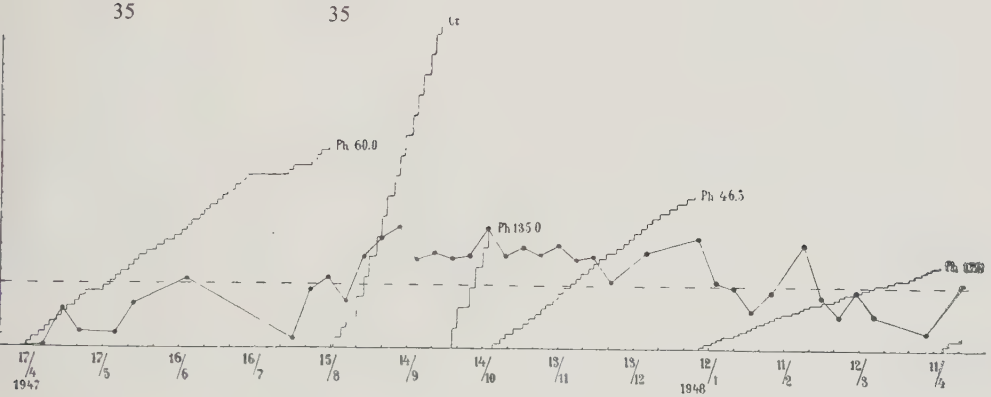
Year and month	1946.4-1946.9		1946.10-1947.4		1947.8	-1947.10	1948.1	1948.4	1948.5
Age	19.6	19.11	20.0	20.6	20.10	21.0	21.3	21.6	21.7
Physex	90.0			60.0	135.0	46.5	17.0	9.0	
Testosterone propionate									
Thyroid extract			100-200-50						
Concentration of phosphatase	"0" about 5		"0"	<1 about 5		5-10 about 5		1-5 about 5	
Type of sexual maturation	Imitation subtotal			Imitation total					
Volume of testes	<1	1.3	about 1			1.8		1.9	
Diameter of penis		21	17			20		23	
Length of penis		44	46			62		54	
Pubes		2	2			5		4	
Terminal growth of hair		1	1			2		2	
Height	129		133	133	135	137		139	
Height when sitting	62		65	64	66	67		67	
Weight	32		33	31	33	36		37	



1948.8 -1948.11		1949.1
21.10		22.3

0.98

<1	1-5	<1
1.0		1.6
22		21
56		68
4	4	4
3	3	2
138		139
67		67
35		35



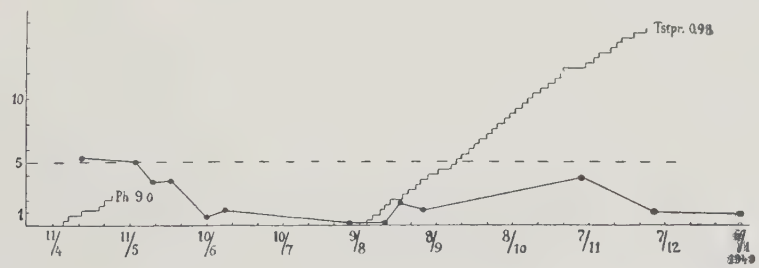


Figure 24. (continued)

Patient No. 97. **Infantilismus primarius.**

Year and month	1946.4-1946.7		1946.8	1946.9-1946.11		1947.1	1947.5	1948.4
Age	14.1	14.4	14.5	14.6	14.8	14.10	15.2	16.1
Physex	43.5		1.5	45.0				
Concentration of phosphatase	"0"	about 5		1-5	about 5	1-5	5-10	about 5
Type of sexual maturation	provoked puberty subtotal + imitation total			Imitation total			spontaneous puberty total	
Volume of testes	2.6	2.2		3.2	3.5		8.4	9.2
Diameter of penis	15	25		22	26		26	24
Lenght of penis	21	43		45	52		60	
Pubes	0	2		2	3		3	4
Terminal growth of hair	0	1		2	2		2	2
Height	159	162		162	164		168	172
Height when sitting	76	79		76	75		82	84
Weight	54	62		62	64		65	72

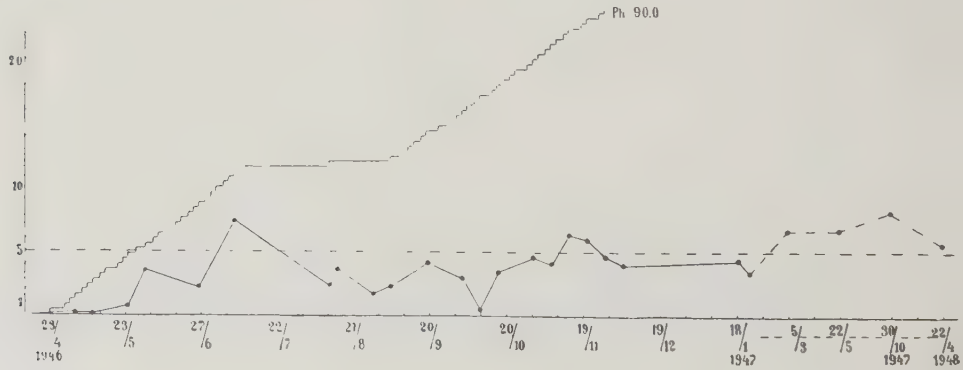


Figure 24. (continued)

Patient No. 119. **Dystrofia adiposo-genitalis.**

Year and month	1946.7-1946.11		1947.4	1947.11
Age	12.1	12.5	12.10	13.5
Physex	67.5			
Concentration of phosphatase	"0"	about 5	1-5*)	about 5
Type of sexual maturation	provoked puberty subtotal			
Volume of testes	d+3.3	6.2	10.3	14.2
Diameter of penis	15	23	24	26
Length of penis	20	48	51	72
Pubes	0	2	2	3
Terminal growth of hair	0	1	1	1
Height	150	152	156	161
Height when sitting	74	78	79	81
Weight	62	67	66	61

*) Values with intervening gaps.

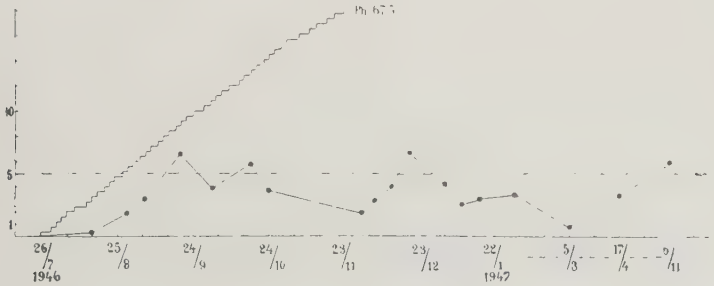


Figure 24. (continued)

Patient No. 123. **Infantilismus primarius.**

Year and month	1946.8-1946.9			1948.1
Age	15.9	15.19		17.2
Physex	30.0			
Concentration of phosphatase	"0"	1-5	?	5-10
Type of sexual maturation	Imitation? provoked puberty? subtotal			spontaneous puberty total
Volume of testes				13.2
Diameter of penis				20
Length of penis				50
Pubes	2			3
Terminal growth of hair	1			1
Height	138			147
Height when sitting	67			70
Weight	33			43

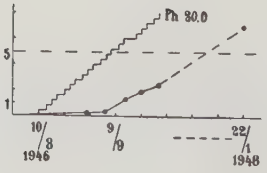


Figure 24. (continued)

Patient No. 126. **Infantilismus secundarius.**

Year and month	1946.1	1947.1-1947.4		1947.6	1947.10-1948.1-1948.4			
Age	18.11	19.3	19.6	19.8	20.0	20.3	20.6	
Physex	7.5	36.0				39.0		
Aminosol (ml)				500	4000			
Concentration of phosphatase	"0"	<1	about5	"0"	"0"	"0"	1-5	"0"
Type of sexual maturation		Imitation subtotal				Imitation subtol		
Volume of testes			1.0			about 1	1.6	
Diameter of penis			23				21	
Length of penis			50				56	
Pubes	0		2			2	3	
Terminal growth of hair	0		1			1	1	
Height		114	117	118	119	119	121	
Height when sitting		55	58	58	58	59	60	
Weight		28	30	26	30	32	34	

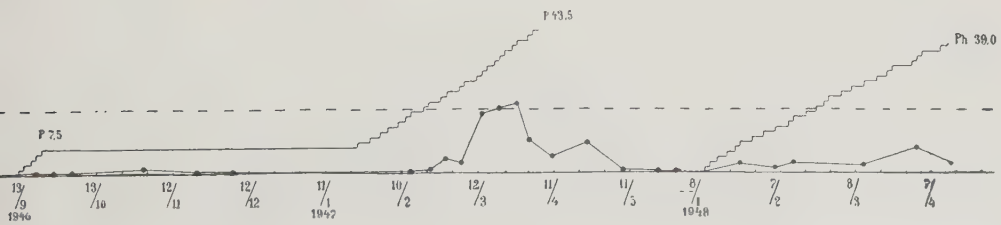


Figure 24. (continued)

Patient No. 128. **Infantilismus secundarius.**

Year and month	1946.10-1946.12		1947.11	1948.11
Age	13.4	13.6	14.5	15.5
Physex	15.0			
Concentration of phosphatase	<1	1-5	1-5	
Type of sexual maturation	provoked puberty subtotal			
Volume of testes	d+s		d+s	d+7.9
Diameter of penis	18		29	28
Length of penis	22		78	80
Pubes	0		2	5
Terminal growth of hair	0		1	2
Height	155		163	171
Height when sitting			79	83
Weight	48		56	66

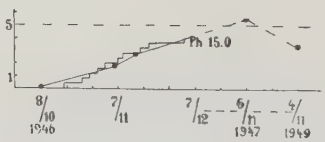


Figure 24. (continued)

Patient No. 134. **Dystrofia adiposo-genitalis.**

Year and month	1946.12-1947.3			1948.1
Age	13.10	14.1		14.11
Physex	45.0			
Concentration of phosphatase	about 1	about 5	about 5	about 10
Type of sexual maturation	spontaneous puberty subtotal	provoked puberty subtotal		spontaneous puberty total
Volume of testes	2.6	3.6		4.5
Diameter of penis	19	21		21
Length of penis	50	62		80
Pubes	3	4		6
Terminal growth of hair	1	1		2
Height	164	166		171
Height when sitting		78		98
Weight	68	72		71

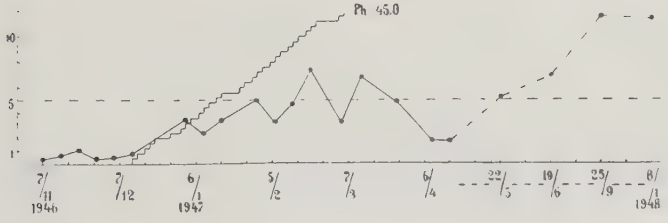


Figure 24. (continued)

Patient No. 136. **Dystrofia adiposo-genitalis.**

Year and month	1946.11	1947.1-1947.3		1947.10	1948.1
Age	13.11	14.1	14.3	14.10	15.1
Physex		36.0			
Concentration of phosphatase		<1 about10	about 10	10-20	10-20
Type of sexual maturation		provoked puberty (sub)total		spontaneous puberty total	
Volume of testes	4.4	5.2			10.0
Diameter of penis	16	23			22
Length of penis	35	64			81
Pubes	2	4		4	3
Terminal growth of hair	1	2		2	3
Height	151	155		160	
Height when sitting	61	73		75	
Weight	59	62		62	

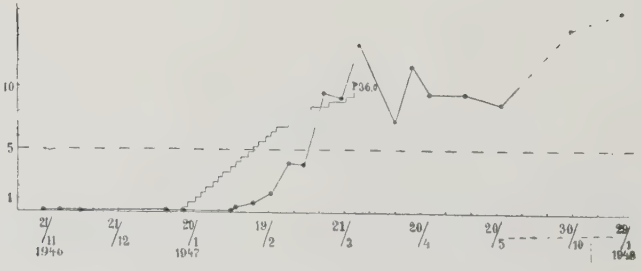
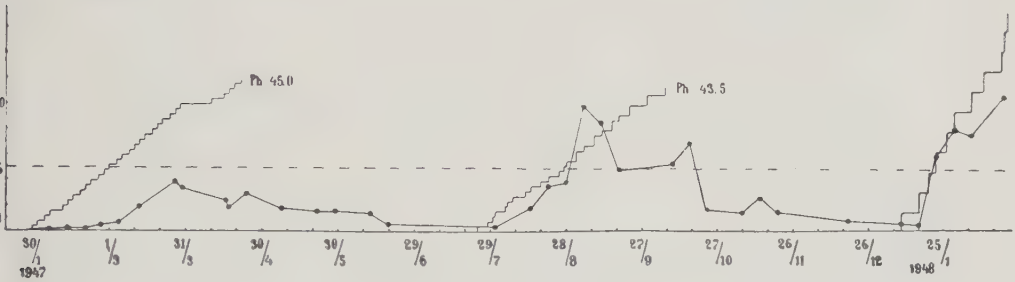
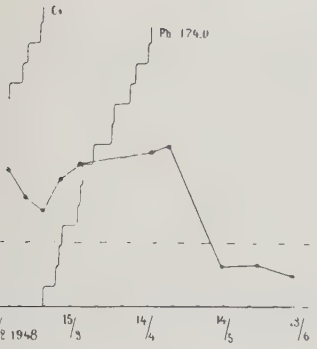


Figure 24. (continued)

Patient No. 149. **Pubertas tarda.**

Year and month	1947.1-1947.4		1947.7 -1947.10		1948.1-1948.4		1948.8-1949.1	
Age	17.5	17.8	17.11	18.2	18.5	18.8	19.0	19.5
Physex	45.0		43.5		174.0			
Methyl testosterone							1.54	
Concentration of phosphatase	"0"	1-5	<1	5-10	< 1	about10	1-5	1-5
Type of sexual maturation	Imitation subtotal		Imitation total		provoked puberty subtotal + imitation total			
Volume of testes	2.7	4.7	3.7	4.7	6.4	5.3	4.5	3.6
Diameter of penis	15	25	20	27	26	30	25	25
Length of penis	35	61	54	70	76	88	64	77
Pubes	0	2	2	3	3	3	4	4
Terminal growth of hair	0	1	1	1	1	1	1	1
Height	168	169	170	172	173	175	176	178
Height when sitting	77	77	78	80	81	81	81	83
Weight	57	64	57	65		71	67	70





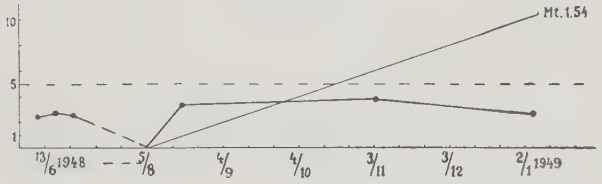


Figure 24. (continued)

Patient No. 151. **Dystrofia adiposo-genitalis.**

Year and month	1947.2	1947.4	1947.5	1947.6	1947.9	1947.12	1948.4	1948.11
Age	14.1	14.3	14.4	14.5	14.8	14 11	15.3	15.10
Physex	46.5				42.0			
Testosterone propionate			0.18					
Concentration of phosphatase	"0"	<1	<1	about 1	<1	1-5	1-5	1-5
Type of sexual maturation	only slight effect				provoked puberty subtotal			
Volume of testes	0.8+s	2.0+s		1.2+s	1.9+s	2.4	5.6	7.9
Diameter of penis		25		25	23	27	25	26
Length of penis		61		73	65	88	83	88
Pubes	2	3		3	3	3	3	4
Terminal growth of hair	1	2		1	2	2	2	3
Height	152	154	155	156	157	160	162	165
Height when sitting		73	74	75	75	77	77	79
Weight	52	54	52	53	50	56	61	58

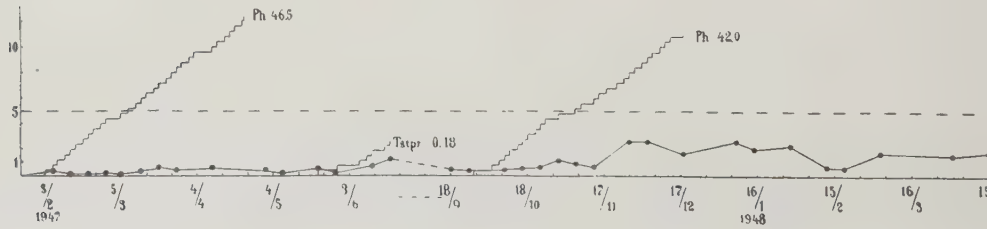


Figure 24. (continued)

Patient No. 153. **(Ejaculate). Eunuchoidism.**

Year and month	1947.3	1947.5	1947.6	1947.9	1947.11	1948.2	1948.4
Age	34.3	34.5	34.6	34.9	34.11	35.2	35.4
Physex	45.0	42.0					
Testosterone propionate							0.84
Methyl testosterone				1.02			
Concentration of phosphatase				Cessation		Cessation	
Type of sexual maturation	Imitation subtotal						
Volume of testes	5.5					4.2	
Diameter of penis	23					23	
Length of penis	66					61	
Pubes	5	5				4	
Terminal growth of hair	3	4				4	

■—■ amount of phosphatase per ejaculate.
+ — + amount of ejaculate in ml.
× — × concentration of phosphatase in ejaculate.

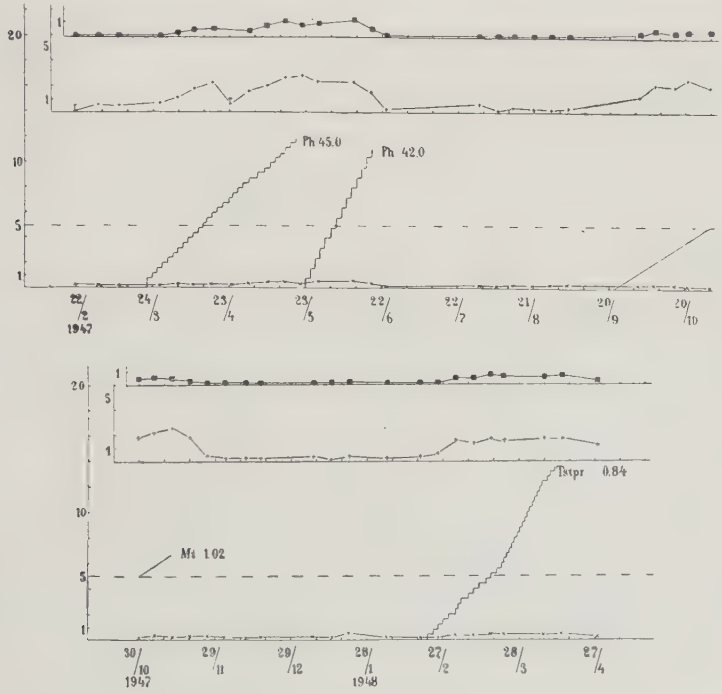


Figure 24. (continued)

Patient No. 164. **Pubertas tarda.**

Year and month		1947.3-1947.7			1947.8
Age		19.1	19.5		19.6
Physex		46.5			
Concentration of phosphatase		1-5	5-10	5-10	about 10
Type of sexual maturation	spontaneous puberty subtotal	provoked puberty total			
Volume of testes		14.5	11.7		12.4
Diameter of penis		30			31
Length of penis		89			108
Pubes		3	3		3
Terminal growth of hair		3	3		3
Height		158	160		161
Height when sitting		76	77		77
Weight		47	52		51

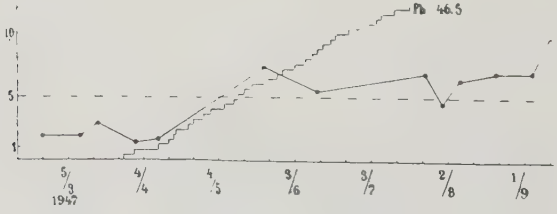
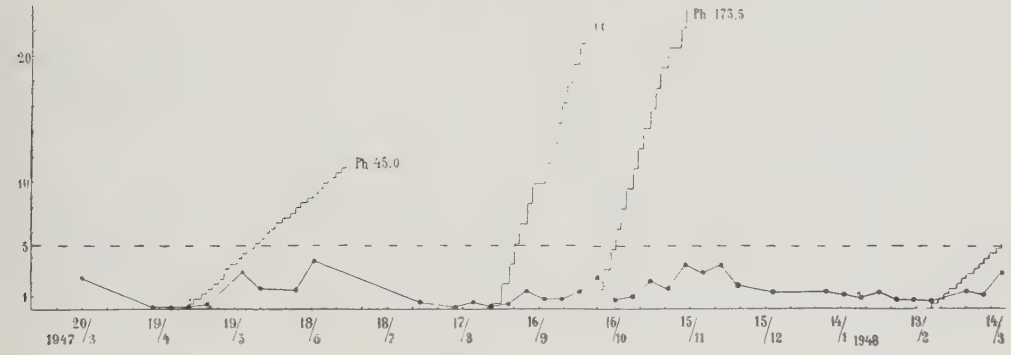


Figure 24. (continued)

Patient No. 165. **Eunuchoidismus.**

Year and month *)	1947.3	1947.5-1947.7		1947.8 -1947.11		1948.2-1948.4		1948.6
Age	36.5	36.7	36.9	36.10	37.1	37.4	37.6	37.8
Physex		45.0		175.5				
Testosterone propionate						0.83		
Concentration of phosphatase	1-5	<1	1-5	<1	1-5	<1	1-5	about 1
Type of sexual maturation		Imitation subtotal		Imitation subtotal				
Volume of testes	5.9				3.2		4.5	
Diameter of penis	20						26	
Length of penis	35						62	
Pubes	4				4		4	
Terminal growth of hair	3				3		3	

*) Last series of physex ended at beginning of February, 1947.



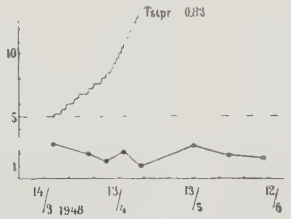


Figure 24. (continued)

Patient No. 170. **Infantilismus primarius.**

Year and month	1947.4-1947.6		1947.8-1947.11		1947.12-1948.1		-1948.3-1948.4		1948.11
Age	15.2	15.4	15.6	15.9	15.10	15.11	16.1	16.2	16.9
Physex	45.0		163.5						
Methyl testosterone					0.5	0.98	1.68		
Concentration of phosphatase	"0"	<1	<1	about 1	<1	<1	about1	about1	about 1
Type of sexual maturation	only slight effect		Imitation subtotal						
Volume of testes	2.0	2.4	3.5	4.7	4.9		4.4		8.3
Diameter of penis	13	23	20	24	24		24		23
Lenght of penis	37	53	50	65	70		74		72
Pubes	0	2	3	3	4		4		5
Terminal growth of hair	0	1	1	2	2		2		2
Height	158	160	161	165	165		170		172
Height when sitting	77	78	78	81	82		84		84
Weight	53	53	53	63	63		68		56

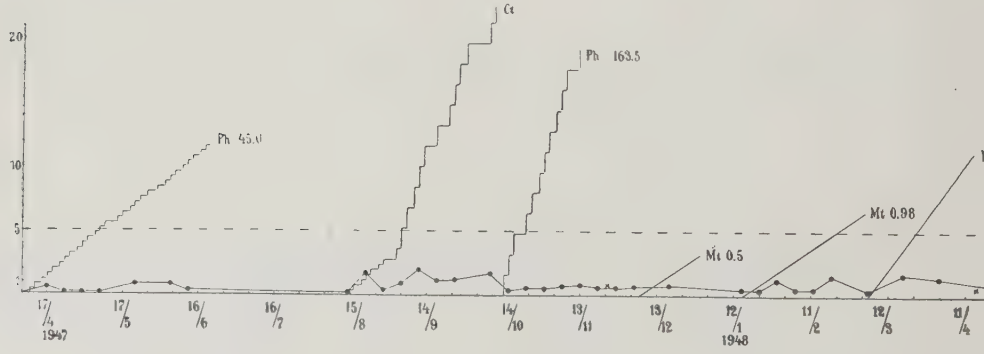


Figure 24. (continued)

Patient No. 189. **Infantilismus primarius.**

Year and month	1947.9-1947.11		1948.3-1948.6		1948.7	1948.11
Age	20.7	20.9	21.1	21.4	21.5	21.9
Physex	33.0		48.0			
Concentration of phosphatase		5-10	1-5	5-10	1-5	1-5
Type of sexual maturation	spontaneous? provoked? puberty subtotal + imitation total		Imitation total			
Volume of testes		9.8	5.2	8.9		
Diameter of penis		28	27	31		
Length of penis		71	64	89		
Pubes		4	4	4		
Terminal growth of hair		1	1	2		
Height		155		155	156	
Height when sitting		76		78	76	
Weight		50		53	57	

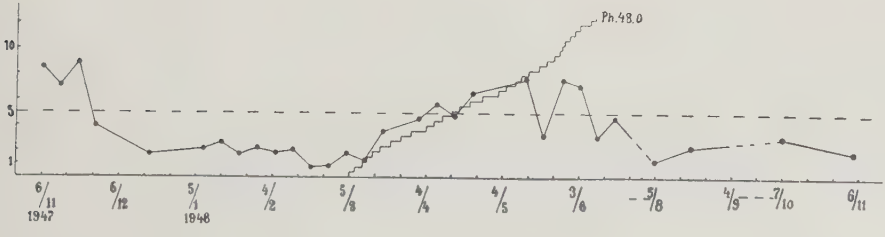


Figure 24. (continued)

Patient No. 191. **Pubertas tarda.**

Year and month	1948.1-1948.4		1948.11
Age	16.3	16.6	17.1
Physex	45.0		
Concentration of phosphatase	"0" about 5		1-5
Type of sexual maturation	Provoked puberty + imitation subtotal		
Volume of testes	6.4	7.5	10.5
Diameter of penis	17	26	26
Length of penis	48	83	74
Pubes	1	3	3
Terminal growth of hair	0	1	1
Height	155	157	161
Height when sitting	72	74	76
Weight	45	54	54

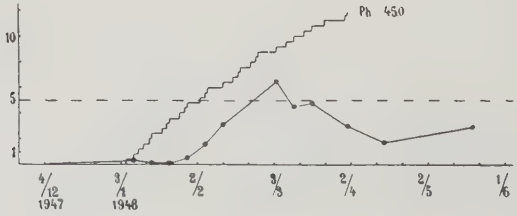


Figure 24. (continued)

Patient No. 192. **Infantilismus secundarius.**

Year and month	1948.1-1948.4		1948.8	1948.11
Age	15.3	15.6	15.10	16.1
Physex	43.5			
Concentration of phosphatase	"0" about 20	10-20	10-15	
Type of sexual maturation	provoked puberty total			
Volume of testes	6.6	5.9	10.9	12.0
Diameter of penis	20	29	26	25
Lenght of penis	51	78	77	71
Pubes	1	2	4	3
Terminal growth of hair	0	1	1	1
Height	148		154	156
Height when sitting	68		73	74
Weight			43	47

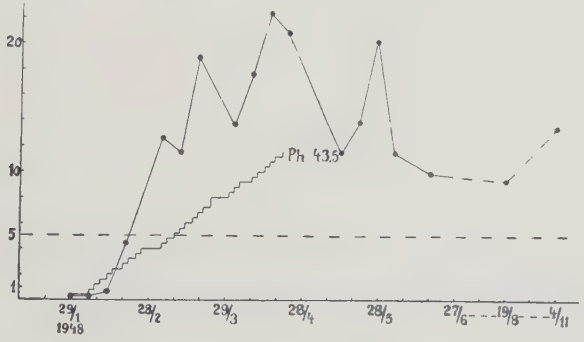


Figure 24. (continued)

Patient No. 193. **Dystrofia adiposo-genitalis.**

Year and month	1948.3-1948.5		1948.8	1948.11
Age	11.9	11.11	12.2	12.5
Physex	43.3			
Concentration of phosphatase	"0" about 5		1-5	1-5
Type of sexual maturation	Provoked puberty subtotal + imitation subtotal			
Volume of testes	1.0	1.4	2.6	
Diameter of penis	14	23	21	
Length of penis	24	52	48	
Pubes	0	3	4	
Terminal growth of hair	0	1	1	
Height		141	144	
Height when sitting		68	70	
Weight		44	45	

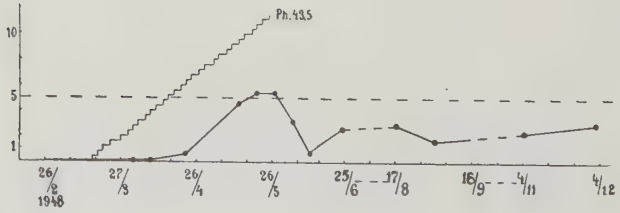


Figure 24. (contiuned)

Patient No. 194. **Infantilismus primarius.**

Year and month	1948.3-1948.6			1948.8-1948.10		1949.1
Age	18.7	18.10		19.0	19.2	19.5
Physex	28.5			45.0		
Concentration of phosphatase	"0"	1-5	<1	<1	1-5	1-5
Type of sexual maturation	Imitation subtotal			Provoked puberty subtotal		
Volume of testes	about 1	1.7		1.5	2.5	3.3
Diameter of penis	14	17		19	22	23
Length of penis	27	50		53	77	65
Pubes	0	3		3	3	3
Terminal growth of hair	0	1		1	1	1
Height	143	146		146	147	149
Height when sitting	68	68		68	70	71
Weight	41	44		45	47	46

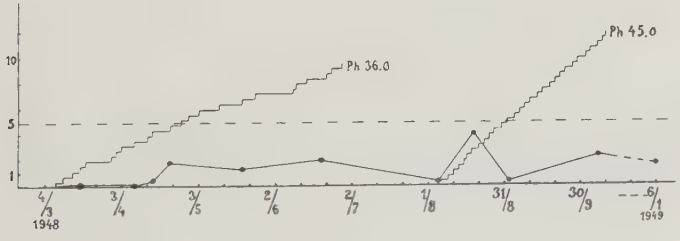


Figure 24. (continued)

Patient No. 196. **Infantilismus primarius.**

Year and month	1948.3-1948.6		1948.8	1948.10-1948.11		1948.12	1949.1
Age	13.6	13.9	13.11	14.1	14.2	14.3	14.4
Physex	43.5			24.0			
Concentration of phosphatase	"0"	1-5	<1	"0"	(>?)1		<1
Type of sexual maturation	Imitation subtotal			Imitation subtotal			
Volume of testes	1.8	1.6		1.6	2.3	2.3	
Diameter of penis	21	23		19	22	22	
Length of penis	37	60		46	52	52	
Pubes	0	1		2	2	2	
Terminal growth of hair	0	0		1	1	1	
Height	137	139	140	140	141	141	
Height when sitting	68	68	69	70	71	71	
Weight	43	43	42	46	48	48	

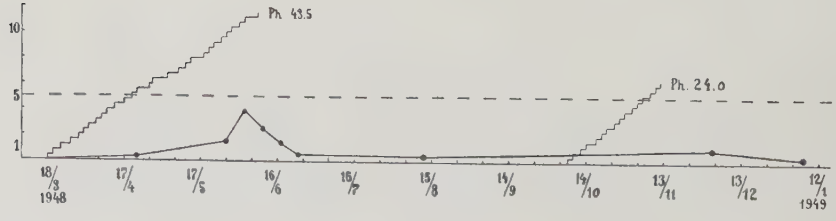


Table XXVII

Course of Sexual Maturation in 16 Individuals with hypandroid Signs (cf. Fig. 24).

	Response to first series, or spontaneous course	Response to next series, or spontaneous course
1.	Imitation subtotal	
2.	Imitation subtotal	Imitation subtotal
3.	Imitation subtotal	Imitation subtotal
4.	Imitation subtotal	Imitation subtotal
5.	Imitation subtotal	Imitation total
6.	Imitation subtotal	Imitation total
7.	Imitation subtotal	Imitation total
8.	Imitation subtotal	Provoked puberty subtotal
9.	Imitation subtotal	Provoked puberty subtotal
10.	Provoked puberty subtotal	
11.	Provoked puberty subtotal	Spontaneous puberty total
12.	Provoked puberty subtotal + Imitation subtotal	
13.	Provoked puberty subtotal + Imitation subtotal	Imitation total
14.	Provoked puberty subtotal	Provoked puberty subtotal + Imitation total
15.	Provoked puberty total	
16.	Spontaneous puberty subtotal	Provoked puberty subtotal
17.	Spontaneous puberty subtotal	Provoked puberty subtotal
18.	Spontaneous puberty subtotal	Provoked puberty
19.	Spontaneous puberty subtotal	?
20.	Spontaneous? Provoked? puberty subtotal	Imitation subtotal
21.	Spontaneous? Provoked? puberty subtotal + Imitation subtotal	Imitation total
22.	Spontaneous? Provoked? puberty subtotal + Imitation subtotal	Imitation total
	subtotal	Spontaneous puberty total

*) A preceding series exerted a very slight effect on the concen tration of phosphatase.

⁰) The fourth series showed: imitation subtotal.

!) The phosphatase reaction not followed during the first (or or two) series.

Response to next series, or spontaneous course	Adiposogenital dystrophy (patient No.)	Infantilism (patient No.)
		42 ! -153 ! -170*)
		36 ! -126-165 ! -196
Imitation subtotal		54⁰)
Spontaneous puberty total		55 !
Imitation total		79
Provoked puberty subtotal		149
+ Imitation total		
Spontaneous puberty total		8 !
		7 ! -194
Provoked puberty subtotal		49
	119-151 !*)	128 !
	35-70-136	
	193	191
Spontaneous puberty total		97
Spontaneous puberty total	68	
		192
Imitation subtotal	66	
Spontaneous puberty total	134	
Spontaneous puberty total	63	
	59 !	
		74-164
		12 ! -189 !
Spontaneous puberty total		41 !
		123
Total:	11	25

Table XXVIII

Number of Patients who arrived at the various Degrees of Sexual Maturity (cf. Table XXVII).

Nature of Sexual Maturity	
Imitation but no puberty	
(Provoked or spontaneous) puberty subtotal	
(Provoked or spontaneous) puberty total	
	Total
Imitation but no puberty	
Provoked but not spontaneous puberty (subtotal or total)	
Spontaneous puberty (subtotal or total)	
(Type of maturation doubtful)	
	Total
Initial Result:—	*Ultimate Result:—*
Imitation	no puberty
Imitation	provoked puberty
Imitation	spontaneous puberty
Provoked puberty subtotal	no spontaneous puberty
Provoked puberty subtotal	spontaneous puberty
Spontaneus puberty subtotal	
(Initial type of maturation doubtful)	
	Total
Imitation (9 patients of infantilism group):—	no puberty
Imitation (6 patients of infantilism group):—	spontaneous or provoked puberty
Provoked puberty subtotal (3 patients of infantilism group):—	no spontaneous puberty
Provoked puberty subtotal (3 patients suffering from adiposo-genital dystrophia):—	no spontaneous puberty

Adiposo-genital dystrophy (number)	Infantilism (number)
—	9
5	7
6	9
11	25
—	9
3	7
7	7
(1)	(2)
11	25
—	9
—	4
—	2
3	3
4	1
3	2
(1)	(4)
11	25

The patients grouped according to age:—

12	*14*	*16*	*18*	*20*	*22*	*24*	*år*
	1	1	1	1	3	2	
		2	3			1	
	1	2					
2	1						

Chapter XVIII.

RELATION BETWEEN TYPE OF PUBERTY AND DEGREE OF SEXUAL MATURITY ATTAINED

In the following it will be examined to what extent the somatic sexual maturity is influenced by the different types of puberty.

Table XXIX shows the final results obtained for certain types of sex character. A comparison between these and the phosphatase reaction is rendered difficult by the inhomogeneity of the series: the patients are of different ages, they have been treated

Table XXIX

Thirty-six Patients with hypandroid Signs treated with Chorionic Gonadotropin, grouped partly according to the Degree of Maturation achieved, partly according to Diagnosis, Sex Characters, Age, and total Administration of Chorionic Gonadotropin at End of Period of Observation (cf. Table XXVIII).

Maturation achieved	Number of patients			Volume of testes in ml			Diameter of penis in mm			Length of penis in mm				
	Total	Adiposo-genital dystrophy	Infantilism	2		≧ 10	25		≧ 30	60	70	80	≧ 90	
Imitation only	9	—	9	3	5	1	6	2	1	2	3	3	—	1
Puberty subtotal	12	5	7	1	7	3	2	8	2	2	2	5	3	—
Puberty total	15	6	9	—	2	13	7	4	4	1	1	4	5	4

Spontaneous puberty total after end of treatment	Adiposogenital dystrophy	Infantilism
in patients (Nos.):	35-63-68-70-134-136	8-41-55-97-123
at ages of:	17-13-14-14-14 -14	18-17-17-15-16

moreover with testosterone and equine gonadotropin, and the observations were finally discontinued at moments when the sex characters of some of the patients were still developing.

It must be assumed in advance that the somatic sexual maturity attained is associated with the production of phosphatase in such a manner that spontaneous total puberty will afford the most advanced development of the sex characters, that provoked total puberty will afford as good, or, perhaps, slightly inferior, results, that subtotal puberty will cause a fainter sexual maturity, and that imitation of puberty will yield the most inferior results.

The correctness of this assumption has been tested by recording the patients' ages, volumes of the testes, dimensions of penis, the degrees of growth of terminal hair and pubes at the end of the observation for the three chief types: imitation of puberty, subtotal puberty, total puberty. It appears then that the first group (imitation alone) has been treated with the largest quantities of chorionic gonadotropin, and the third group (total puberty) with the smallest doses. The patients of Group 1 are the oldest, two-thirds of them being over 20 years old, whereas

Pubes					Terminal growth of hair				Ages							Total administration of chorionic gonadotropin in 1000 I. U.				
2	3	4	5	6	1	2	3	4	12	14	16	18	20	22	≥ 24	5	100	150	≥ 200	
1	1	4	1	2	3	3	2	1	—	1	1	1	1	3	2	—	2	1	—	6
1	4	4	2	1	6	3	2	1	2	3	2	2	1	—	2	4	5	1	—	2
—	4	4	3	4	3	6	5	1	—	5	5	5	—	—	—	9	4	1	—	—

those of the third group are all between 14 and 20 years old. Despite the comparatively advanced age of the patients the volume of the testes was smallest in the first group, largest in the third group.

The length of the penis in the patients who have merely reached imitation of puberty is small in most cases. Measurements of the diameter of the penis showed no unquestionable tendency.

In the group of total puberty the growth of pubes is more frequently found to be of normal or almost normal intensity than in the other two groups. When the age distribution is considered, this difference becomes more obvious.

Only one patient in each group has got strong growth of beard. In Group 3 the rare incidence of this sex characteristic is explicable by the age, but among normal individuals with the same age distribution as in Group 1 the growth of beard would in most cases have been intense. Similarly, the frequency of intense growth of beard expected according to age in Group 2 is greater than the one actually found.

One more observation may be mentioned: All the six patients suffering from adiposogenital dystrophy in the third group have reached spontaneous puberty, but only 5 out of the 8 patients of the infantilism group. Table XXVIII shows the ages of the patients at the time of occurrence of spontaneous puberty. It appears from the table that the latter seem to reach spontaneous puberty later than do the former (see also page 161 and Table XX).

Conclusion.

The hypothesis that the degree of development of the sex characters is related to the type of puberty (imitation of puberty, subtotal or total puberty) juged on the basis of the phosphatase reaction proves correct, if the volume of the testes, the length of the penis, the degree of development of the pubes and the growth of terminal hair are made the basis of the estimate of the degree of sexual maturity.

The statement further shows that it must be regarded as probable that, if the patient belongs to the infantilism group, is more than 20 years old, and his testes despite intensive treatment are small, chorionic gonadotropin can only give rise to imitation of puberty.

Chapter XIX

INFLUENCE OF CHORIONIC GONADOTROPIN TREATMENT ON THE PHOSPHATASE CONCENTRATION AND ON THE EXCRETION IN URINE OF GONADOTROPIC, ANDROGENIC AND OESTROGENIC SUBSTANCES

Previous Examinations of the Excretion of Hormones influenced by Chorionic Gonadotropin.

Investigations of this kind require many analyses of various 24-hours-portions of urine, because the values found vary very much from day to day (Koch, 1937, Pedersen-Bjergaard and Tønnesen, 1948).

The first examinations of the excretion of hormones in the urine during treatment with chorionic gonadotropin were made by Sand and Plum (1938) who found that from 2 to 7 per cent. of the amount of hormone injected were excreted in the urine. In two of the three cases examined — all of them boys suffering from adiposogenital dystrophy — increased androgenuria was found. The analyses were made with 72-hours-portions but, nevertheless, showed fairly great, irregular variations. The curves plotted for both these patients shows that the androgenuria after discontinuance of the treatment seems to persist at the attained level, whereas the gonadotropinuria falls to the same low values as prior to treatment.

Schonfeld (1943) recommends a prognosticating treatment with 500 to 700 I. U. 3 times a week for 2 to 3 weeks, rising, if indicated, to 1500 I. U. and, at the same time, control of the androgenuria, but he does not mention the results which this experiments may have afforded.

Writer's Examinations.

Six patients (Nos. 153, 164, 165, 170, 174, and 192) were examined for production of phosphatase and for the renal excretion of gonadotropins, androgens (determined biometrically and photometrically) and oestrogens before, during, and after treatment with chorionic gonadotropin, Nos. 165 and 174 during treatment with testosterone propionate too. Patient No. 174 suffered from adiposogenital dystrophy, whereas the other five patients were of the infantilism group.

Table XXX

The table shows the renal excretion of gonadotropic, oestrogenic and androgenic hormones in 24 hours with level of the concentration of phosphatase in 6 hypandrogenic patients (Nos. 153, 164, 165, 170, 174 and 192) before, during and after treatment with chorionic gonadotropin, respectively testosterone propionate. The hormonal excretion was determined in the the total urine of 2 × 24 hours (consecutive). The table states the dates of the last collection of urine.

The values for the hormonal excretion are, respectively, rat units (gonadotropic), mouse units (oestrogenic) and international units (androgenic hormone).

With regard to the technique employed in the hormonal analyses, see page 54.

As to the single determinations of the concentration of phosphatase and the exact dates when treatment was instituted and concluded, reference may be made to Fig. 24.

No. 153. Eunuchoidism.

Date	Gonado-tropin	Oestro-gens	Androgens photo-metric	Androgens bio-metric	Treatment	Concen-tration of phospha-tase in expr. secr. (see Fig. 24)	Type of sexual maturation
17.3.47	45	<8	35	25			
20.3	7.5	<8	25	17.5			
27.3	45	<8	47	35			
1.4	30	33	57	25.5			
9.4	90	33	35.5	10			
16.4	10	33	43	20			
23.4	45	33	40	20			
30.4	10	33	20	10	Physex		Imitation
7.5	25	11	30	15	87.000 I.U.		subtotal
21.5	90	33	50	25			
28.5	10	67	80	100			
11.6	15	33	75	50			
18.6	25	33	105				
24.7	25	33	30	10			
6.8	<5	<8	70	35			
20.8	<5	<8	45	30			
3.9	<5	<8	40	15			

No. 164. Pubertas tarda.

Table XXX (cont.)

Date	Gonado-tropin	Oestro-gens	Androgens photo-metric	Androgens bio-metric	Treatment	Concentration of phosphatase in expr. secr. (see Fig. 24)	Type of sexual maturation
26.2.47	<5	11	10	5			spontaneous puberty
26.3	<5	8	20	20		1—<5	subtotal
31.3	45	11	62	25			
10.4	7.5	<8	56	10			
16.4	10	17	5	4.5			
23.4	10	11	25	15			
29.4	10	50	45	30	Physex		provoked
9.5	10	11	30	10	46.500 I.U.		puberty
28.5	25	11	30	20			total
4.6	10	17	20	10			
10.6	10	<8	60	30			
18.6	10	33	70	20		5—<10	
24.7	<7.5	<8	85	25			
30.7	45	<8	25	10			
6.8	10	<8	30	10			
12,8	<7.5	<8	45	20			
26.8	<5	<8	20	15			
3.9	<5	<8	40				
10.0	<5	<8	40	10			
24.9	<5	<8	<2.5	<2.5			
15.10	<5	<8	10	<2.5		about 10	

Each hormone analysis was made with the total portion of urine of 2 consecutive days.

The results, which are shown in Tables XXX and XXXI, will be discussed in the following.

No. 153: Eunuchoidism. No unquestionable effect on the excretion of either gonadotropin or androgen. On the other hand, pronounced increase of oestrogenuria throughout the treatment.

Moderate increase of the volume of the ejaculate, but only a very slight rise of its phosphatase concentration which was very low before treatment. The effect stopped with the treatment.

No. 164: Pubertas tarda. Slight increase of gonadotropinuria. Very high, though varying values for the androgenuria which, after the discontinuance of the treatment, fell to the initial values.

The treatment caused a permanent improvement of the phosphatase concentration, which became normal.

No. 165. Eunuchoidism.

Table XXX (cont.)

Date	Gonadotropin	Oestrogens	Androgens photometric	Androgens biometric	Treatment	Concentration of phosphatase in expr. secr. (see Fig. 24)	Type of sexual maturation
24.3.47	<5	<8	35	25		1— <5	
30.3	<5	<8	43	10			
22.4	<5	<8	30	10			
26.4	<5	<8	50	15		<1	
4.5	10	<8	75	25			
13.5	25	11	<2.5	5	Physex 45.000 I.U.		Imitation subtotal
28.5	10	<8	75	45			
11.6	25	<8	45	15			
17.6	10	<8	125	45		1— <5	
24.7	<5	<8	55	30			
30.7	<5	<8	30	15			
6.8	<5	<8	35	5			
13.8	5	<8	65	65			
20.8	<5	<8	60	35			
26.8	<7,5	<8	70	60		<1	
3.9	90	<8	45	30			
11.9	90	<8	86	65			
16.9	45	11	105	5			
22.9	180	<8	60	15			
28.9	90	<8	45				
8.10	45	<8	35	5	Physex 175.500 I.U.		Imitation subtotal
13.10	45	8	10	2.5			
20.10	10	<8	<2.5	2.5			
27.10	180	33	<2.5	5			
4.11	90	<8	60	10			
10.11	90	<8	90	20		1—<5	
17.11	90	<8	40	10			
24.11	<10	11	15	5			
1.12	7.5	<8	5	2.5			
8.12	<5	<8	45	5			
14.12	<5	<8	20	5			
4.1.48	45	<8	30	10			
11.1	10	<8	15	1			
18.1	<5	<8	≦ 2.5	≦ 2.5			
25.1	<5	<8	40	10			
1.2	5	<8	45	10			
7.2	5	<8	60	15			
16.2	5	11	7.5	5		<1	
21.2	10	11	35	10			
29.2	10	<8	<2.5	5			
8.3	<5	33	95	25			
15.3	<5	17	20	20	Testosterone propionate 0.825 g		
26.3	5	11	25	20			
3.4	<5	33	85	35			
10.4	<5	33	7.5	30			
18.4	10	11	125	35		1—<5	
8.5	<5		7.5	10			
23.5	<5	11	25	25			
8.6	5		<2.5	≦ 2.5		about 1	

No. 170. Infantilismus primarius. **Table XXX (cont.)**

Date	Gonadotropin	Oestrogens	Androgens photometric	Androgens biometric	Treatment	Concentration of phosphatase ejaculate (see Fig. 24)	Type of sexual maturation
25.3.47	7.5	<8	<5	5			
1.4	<5	<8	10	<2.5			
9.4	<5	<8	33	4		"0"	
13.4	10	11	5	4			
21.4	45	<8	25	10			
28.4	15	11		15			
10.5	<5	11	30	5	Physex 45.000 I.U.		very slight effect
27.5	25	33	20	5			
8.6	25	11	40	10			
15.6	25	<8	70	50		<1	
6.8	<5	<8	50	20			
10.8		<8	40	15		<1	
18.8	90	<8	40	25			
26.8	45	<8	20	10			
7.9	180	<8	37	35	Physex		Imitation
28.9	90	33	30	10	163.500 I.U.		subtotat
27.10	10	33	<2.5	2.5			
18.11	90	<8	10	2.5		about 1	
9.12	<5	<8	25	5		about 1	

No. 165: Eunuchoidism. No unquestionable effect on either androgenuria or oestrogenuria. On the other hand, a rise of the gonadotropinuria, which was greater during the intense treatment with chorionic gonadotropin. During treatment with testosterone propionate a pronounced increase of the oestrogenuria was observed, but no influence on the excretion of the other hormones.

Each treatment produced a temporary rise of the phosphatase concentration, though only to subnormal values.

No. 170: Primary infantilism. No unquestionable effect on the androgenuria, but an increase of the gonadotropinuria, greatest during the intensive treatment. Also, temporary increase of the oestrogenuria.

Very slight transient rise of the phosphatase concentration during each treatment.

No. 174: Adiposogenital dystrophy. No unquestionable effect on the androgenuria either during the brief treatment with chorionic gonadotropin or during the course of testo-

No. 174. Dystrofia-adiposo genitalis·

Table XXX (cont.)

Date	Gonado-tropin	Oestro-gens	Androgens photo-metric	Androgens bio-metric	Treatment	Concen-tration of phospha-tase in ejaculate (see Fig. 24)	Type of sexual maturation
27.4.47	<5	<8	20	10			
3.5	<5	<8	70	25		"0"	
12.5	25	<8	55	25			
27.5	10	11	25	15	Physex		no effect
31.5	10	17	60	20	25.500 I.U.		
8.6	45	11	50	15		<1	
14.9	<5	<8	40	5			
21,9	<5	<8	40	<2.5			
28.9	<5	<8	25	2.5		<1	
5.10	<5	<8	65	20			
13.10	<5	8	<2.5	2.5			
19.10	<5	17	<2.5	5			
26.10	<5	33	<2.5	2.5			
2.11	<5	<8	15	5	Testosterone		
9.11	10	<8	20	5	propionate		
15.11	<5	11	10	5	0.750 g		
23.11	<5	<8	15	5			
1.12	<5	<8	<2.5	<2.5			
7.12	<10	<8					
14.12	<5	<8	15	5		5—10	
4.1.48	45	<8	<2.5	<2.5			
11.1	7.5	<8	<2.5	<2.5			
18.1	<5	<8	<2.5	<2.5			
25.1	<5	<8	5	≦2.5			
1.2	25	<8	<2.5	<2.5			
8.2	7.5	<8	5	2.5			
15.2	75	<8	<2.5	<2.5			
29.2	<5	<8	40	25			
14.3	<5	<8	<2.5	<0.5			
4.4	5	11	20	0.5			
23.5	<5	11	<2.5	0.5		1—<5	

sterone propionate. On the other hand, a slight increase of the oestrogenuria both during the first and the last treatment. Moreover, a slight, transient increase of the gonadotropinuria during the first treatment, strangely enough also immediately after discontinuance of the treatment with testosterone.

During the brief treatment with chorionic gonadotropin the production of secretion but not that of phosphatase, was started. The phosphatase concentration rose to normal values during the treatment with testosterone and subsequently decreased, though — what is remarkable — not to 0, but to values between 1 and

No. 192. Infantilismus secundarius. **Table XXX (cont.)**

Date	Gonadotropin	Oestrogens	Androgens photometric	Androgens biometric	Treatment	Concentration of phosphatase in ejaculate (see fig. 24)	Type of sexual maturation
11.1.48	5	<8	<2.5	<2.5			
18.1	<5	<8	<2.5	≦ 2.5			
25.1	5	<8	5	≦ 2.5		"0"	
1.2	180	<8	15	<2.5			
8.2	180	11	20	5			
15.2	180	11	40	5			
22.2	180	67	10	10			provoked
7.3	450	11	70	20	Physex		puberty
14.3	180	67	10	5	43.500 I.U.		total
5.4	180	67	65	35			
11.4	180	150	30	15			
18.4	450	100	110	50		about 20	
16.5	<5	< 8	25	15			
23.5	<5	11	15	10			
30.5	<5	<8	15	5			
13.6	<5	<8	45	20		10 – 15	

2 K. P. U., which were retained during the subsequent months.

No. 192: Infantilism. Distinct increase of the androgenuria, both when measured biometrically and photometrically. The values apparently remained at the level attained even after discontinuance of the treatment. Moreover, pronounced increase both of gonadotropinuria and oestrogenuria, though these two qualities increased but temporarily during the treatment.

The phosphatase concentration rose during the treatment from 0 to fully normal values, which became permanent.

The Phosphatase Reaction and Gonadotropinuria.

A certain increase of the gonadotropinuria was observed in all the patients treated with chorionic gonadotropin with the exception of patient No. 153. The increase stopped at the same time as the treatment was terminated, also in Nos. 164 and 192, in whom the production of phosphatase continued.

It is peculiar that the gonadotropinuria in No. 174 shortly after discontinuance of the treatment with testosterone increased temporarily, and that the production of phosphatase continued, although with a lower intensity than during treatment. It is impossible to say whether these two phenomena are

Table XXXI

The Phosphatase Reaction and the Renal Excretion of Gonadotropins, Androgens and Oestrogens in Connection with Treatment of 6 hypandrogenic Patients with Chorionic Gonadotropin, respectively Testosterone; cf. Table XXX.

No.	Treatment		Gonadotropinuria		Androgenuria		Oestrogenuria		Concentration of phosphatase		
	chorionic gonadotropin	testosterone propionate	rise during treatment	continuing after treatment has closed	rise during treatment	continuing after treatment has ceased	rise during treatment	continuing after treatment has ceased	rise during treatment	continuing after treatment has ceased	normal during treatment
153	+						+		+		
164	+		(+)		+		(+)		+	+	+
165	+		+						+		
—		+					+		+		
170	+		+				+		+		
174	+		+				+				
—		+	(+)				+		+		+
192	+		+		+	+	+		+	+	+

causally connected and are due to the treatment with testosterone. No. 165, who was subjected to a still more vigorous treatment with testosterone, did not display hypergonadotropinuria either during or after the treatment.

The Phosphatase Reaction and Androgenuria.

In all the six patients except No. 174 the treatment with chorionic gonadotropin brought about a rise of the phosphatase concentration, which, however, became normal only in Nos. 164 and 192. These two are the only patients who, during the treatment, displayed an increase of the androgenuria, and the only ones in whom the attained level of the phosphatase concentration persisted after discontinuance of the treatment. Correspondingly, No. 192 retained the increased androgenuria values. On the other hand, after the treatment No. 164 showed a decrease of the androgenuria values. The production of phosphatase can thus be stimulated with chorionic gonadotropin, whilst at the same time the necessary increase of the production of testis hormone need not manifest itself by increased androgenuria.

The Phosphatase Reaction and Oestrogenuria.

With the exception of No. 165 all the six patients treated with gonadotropin displayed oestrogenuria during the treatment. In all the five patients the increase was temporary, even in the two, Nos. 164 and 192, who had a permanent increase of the production of phosphatase.

It is remarkable that the treatment with testosterone in patient No. 165 caused an increase of the oestrogenuria, which the very intensive treatment with chorionic gonadotropin had failed to produce. The two treatments resulted in identical phosphatase concentrations.

Both after the treatment with testosterone and after the brief treatment with chorionic gonadotropin patient No. 174 displayed an increased oestrogenuria. The phosphatase reaction, on the other hand, was very weak during the treatment with chorionic gonadotropin, which probably was of too brief duration to bring about a full effect.

Many of the observations described can only be estimated with sufficient certainty in a larger series of cases. However,

the following may probably be concluded from these findings:

An increase of the androgenuria is a less sensitive criterion for testis stimulation during treatment with chorionic gonadotropin than the rise of a phosphatase concentration that was low before treatment.

An increase of the oestrogenuria is an equally, or more sensitive, criterion for testis stimulation during treatment with chorionic gonadotropin than a rise of the phosphatase concentration.

The stimulation of the testes may have become permanent, which is evident from the rise of the phosphatase concentration persisting after the termination of the treatment despite the cessation of the increased renal excretion of one or several — possibly all — hormones when the treatment is discontinued.

Chapter XX

LINES OF TREATMENT OF HYPANDROGENIC INDIVIDUALS WITH CHORIONIC GONADOTROPIN BASED ON THE PHOSPHATASE REACTION

The question whether treatment with chorionic gonadotropin is indicated in a case of hypandry depends in principle on the intensity of the pituitary output of gonadotropin and the power of the testes to produce androgen.

Pituitary Hypofunction with Regard to the Production of Gonadotropin.

It is generally assumed that treatment with gonadotropin is indicated in cases of reduced production of gonadotropin by the pituitary in which the potential function of the testes is intact. The term stimulation therapy in such cases is correct, if it is applied to testes. In an affection, which primarily is seated in the pituitary and not in the testes, however, it is a stimulation therapy — alternatively a substitution therapy — which is primarily indicated. Any stimulation therapy of the pituitary is not yet known with certainty, however, although Rydberg and Mathiesen (1948) found that dinoestrol treatment of women suffering from amenorrhoea stimulated the production of gonadotropin by the pituitary. In this connection mention may be made of patients No. 165 and No. 174 (Fig. 1) in whom testosterone propionate brought about not only a temporary vigorous production of phosphatase but also a persistent, though weaker, one, and in patient No. 49 (Fig. 24) the increase of the production of phosphatase was retained.

With our present knowledge a treatment with chorionic gona-

dotropin can be characterized as a mere substitution therapy for the pituitary and will, like any other substituting treatment, only be effective as long as the treatment is going on. As has been shown by the phosphatase examinations described, this is the case in the treatment of most patients suffering from infantilism.

Testicular Hypofunction with Regard to the Production of Androgen.

In conditions, in which the pituitary functions apparently are intact, whilst the testicular function is insufficient, i. e. in cases of so-called testicular infantilism or testicular eunuchoidism, treatment with gonadotropin is generally not considered indicated, the reasoning being that the supply of pituitary gonadotropin is greater in advance than normally, which manifests itself by hypergonadotropinuria. This probably does not exclude, however, that an energetic treatment with gonadotropin will exert a still more intense action on the testes, possibly leading to an increased output of testis hormone during the term "stimulation therapy of the testes" must appear just provement of the condition of the testes and, hence, of the production of androgens (provoked puberty). If this may occur, the term "stimulation therapy of the testes" must appear just as adequate for the treatment with chorionic gonadotropin in such cases of isolated testicular hypofunction as for the treatment of the above-mentioned cases of primary pituitary hypofunction with testes which are potentially able to function.

Amount of the Spontaneous Gonadotropinuria and the Phosphatase Response to Chorionic Gonadotropin.

In the total series of hypandrogenic patients treated with chorionic gonadotropin, collected in Fig. 24, the amount of the gonadotropinuria was determined in 14 cases (Nos. 35, 36, 42, 49, 54, 55, 79, 151, 153, 164, 165, 170, 191 and 192). In two of these patients (Nos. 49 and 79), an increased excretion was found (> 25 R.U./24 hours). In both patients the production of phosphatase during the treatment with chorionic gonadotropin increased, though merely to subnormal values during the first course followed with phosphatase analyses. During the second course subtotal puberty was brought about in No. 49 and, in

No. 79, again an imitation, which this time was total. Hypergonadotropinuria thus does not exclude either that the testes react temporarily or that they improve permanently during treatment with chorionic gonadotropin.

In the remaining patients the excretion of gonadotropin was normal. The first examination of patient No. 153, however, disclosed a considerably increased excretion, but this may be due to previous treatment (see Fig. 24). In six of these patients (Nos. 36, 42, 54, 55, 165 and 170) a subtotal imitation only was attained during the first controlled course of treatment with chorionic gonadotropin. One patient (No. 55) subsequently developed spontaneous puberty.

The determination of the gonadotropin thus does not seem to be any reliable aid in the prognosis with regard to the response of the testes to chorionic gonadotropin.

The cause may be that the amount of the gonadotropinuria is a very sensitive criterion for the output of testis hormone, so that a slight reduction of this output entails hypergonadotropinuria. This hypothesis which was put forward by Heller and Nelson (1945), who were unable to demonstrate any correlation between the gonadotropinuria on the one hand and the clinical signs and the excretion of 17-ketosteroids on the other hands, is corroborated by Hamburger and Halvorsen's findings (1942): in two out of twenty-two middle-aged normal men they found hypergonadotropinuria; but the values of the renal androgen excretion of both individuals were low normal.

According to the demonstration above of the fact that chorionic gonadotropin exerts an effect on the production of phosphatase in spite of existing hypergonadotropinuria, it is possible to elucidate Nelson's observation (1934 *b* and 1937) that chorionic gonadotropin increases the output of androgens from artificially cryptorchid testes in spite of the fact that the pituitary of such animals contains more gonadotropin than normally. To explain this appearant discrepancy, which he finds surprising, Nelson put forward the supposition that the pituitary of animals which for a long period have been cryptorchid, contains increased quantities of gonadotropin. However, such an auxiliary hypothesis does not seem necessary to explain the effect of chorionic gonadotropin, because an increased gonadotropinuria, as was shown above, does not exclude

that the testes are sensitive to — eventually reparable under — the influence of large doses of chorionic gonadotropin. Fraser *et al.* (1941) maintained that treatment with chorionic gonadotropin does not give rise to increased excretion of 17-ketosteroids in eunuchoids with hypergonadotropinuria. As is shown in the present book (page 261), the production of phosphatase is more sensitive to chorionic gonadotropin than is the excretion og 17-ketosteroids. The latter thus is too coarse a criterion for registering an influence on testes in all cases.

Response to Chorionic Gonadotropin as Prognostic Criterion.

The estimation of the possible favourable influence of treatment with chorionic gonadotropin in the individual case must be based on the clinical data, possibly also on a therapeutical test. The clinical conditions have been discussed before (Table XXVI). As therapeutical test may be chosen the androgenuria and the phosphatase reaction during and after a course of treatment with chorionic gonadotropin.

The clinical improvement during the treatment might seem to be the most important, but it is in reality fairly uniform whether it has caused puberty or imitation, because in almost all the cases a growth of the penis and the pubes as well as of stature will ensue. Such observations during the first series therefore seldom afford a clue to differentiation with regard to the after-effect of the treatment, which appears from the following survey: among the patients treated with chorionic gonadotropin were 12 who, before treatment, lacked a growth of accessory hair (Nos. 49, 54, 70, 97, 119, 149, 170, 191, 192, 193, 194 and 196 (see Fig. 24)). With the exception of one (No. 196) they all developed pubes during the first course of treatment, 7 of the 12 up to stage "2", 4 (Nos. 70, 191, 193 and 194) up to stage "3", No. 70 moreover developed hirci. Three of the 4 last-mentioned patients reached provoked subtotal puberty (e.g. No. 193, who showed a temporary rise to normal phosphatase concentration), whereas the treatment of No. 191 resulted in subtotal imitation of puberty. Two of the remaining 7 patients (No. 97 and No. 119) obtained provoked subtotal puberty, the rest merely obtaining imitation of puberty. The 5 patients, who obtained provoked puberty, showed little or no growth of the testes during the first course. Thus, whereas the testes do not

afford any prognostic clue, the pubes response is better, as there is a fair chance of provoked puberty if during the first course of treatment the pubes become dense.

Androgenuria during treatment with chorionic gonadotropin was discussed in detail in Chapter XIX.

The production of phosphatase during a course of treatment with chorionic gonadotropin may follow three qualitatively different courses, according to which chorionic gonadotropin with regard to effect can be put in relation to testosterone: —

(1) No production of phosphatase = no production of testis hormone.

Conclusion: Chorionic gonadotropin without effect. Testosterone would have exerted a better effect.

(2) Temporary production of phosphatase = imitation of puberty.

Conclusion: Chorionic gonadotropin affords the same as, possibly less than, testosterone would have done.

(3) Lasting production af phosphatase = provoked puberty.

Conclusion: Chorionic gonadotropin exerts a better effect than testosterone would have done.

re 2. If a fully normal phosphatase concentration is obtained, chorionic gonadotropin affords the same as a treatment with testosterone would have done. If merely a submaximal phosphatase concentration is obtained, it is not sure that treatment with testosterone would have afforded more. As is shown in Fig. 1, it is not always possible, even with large doses of testosterone, to obtain a normal phosphatase concentration, a fact which for the present is inexplicable (see discussion, page 87). However, from the course of such a first series it is only possible with some reservation to draw conclusions concerning the course during subsequent series of chorionic gonadotropin, for, as was shown on page 198, it may happen that the course of the production of phosphatase during the subsequent series undergoes changes (e.g. first series: subtotal imitation, subsequent series: total imitation; or first series: imitation, subsequent series: provoked puberty).

After these reflections about the effect of chorionic gonadotropin the indications will briefly be discussed.

Adiposogenital Dystrophy.

As was mentioned on page 138, the obesity remains uninfluenced by chorionic gonadotropin, which is in complete conformity with the experiences from the present series of cases.

Finally, there are a couple of patients, whose puberty has not commenced at the age of 16 years (see page 137), and who thus demonstrate that their hypandry is not physiological but pathological. It might seem to be well indicated to treat this group of patients before their sixteenth year, but with our present knowledge it is impossible with certainty to decise on the nature of hypandry in a boy suffering from adiposogenital dystrophy who is under 16 years of age. As was emphasized on page 130, the volume of testes is of doubtful value. The majority of our patients suffering from adiposogenital dystrophy presented volumes of the testes between 1.5 and 5 ml when they were between 13 and 16 years of age (see Fig. 24). With the exception of three (Nos. 66, 134 and 151) all the patients subsequently developed a normal volume, namely $\geqq$ 10 ml; two out of the three displayed a slight growth of the testes (No. 134, from 2.6 to 4.5 ml; No. 151, from about 2 to 5.6 ml). The 16-year-old patient, No. 66, did not show unquestionable growth (from 1.5 to about 2 ml). Even in this case chorionic gonadotropin gave rise to subtotal puberty. Continued observation could not be undertaken because of the patient's departure.

Thus there remains the hypandry as the object of treatment. According to the experiences mentioned on page 137, the hypandry in the great majority of these patients seems to be physiological, and puberty occurs spontaneously at the normal time or rather a little earlier. In this work it has been shown that chorionic gonadotropin in a single course of treatment almost infallibly gives rise to puberty. That this effect obtained with chorionic gonadotropin will be superfluous in most cases is evident from the frequently demonstrated, subsequently occurring spontaneous puberty. Thus in the great majority of cases of adiposogenital dystrophy there seems to be no indication for treatment with chorionic gonadotropin.

The Infantilism Group.

As was shown on page 199, chorionic gonadotropin does not

always bring about puberty in such patients, but often merely imitation of puberty. Not infrequently spontaneous puberty occurs in these patients too. If it has not commenced when the patient is 15 to 16 years old, there is but little chance that it will occur spontaneously, and treatment with gonadotropin or testosterone is absolutely indicated. Even in the cases, in which spontaneous puberty ensues later, the treatment has been useful by preventing or inhibiting the development of eunuchoid proportions. In an infantilism patient under 16 years of age the mere fact that chorionic gonadotropin often exerts an accelerating action on his growth of stature (Gordon and Fields, 1942, Horstmann, 1949, and others), will be sufficient for the indication of the treatment and, further, there is a chance — not afforded by testosterone — that the treatment will provoke puberty.

It holds good as a principal rule that treatment with chorionic gonadotropin of these two groups of patients is a therapeutical paradox: The patients suffering from adiposogenital dystrophy are almost bound to obtain provoked puberty by treatment during early puberty or later, in return this effect is superfluous in the majority of cases. Conversely, in the infantilism group, provoked puberty will often be desirable in these patients but is far from always obtainable.

SUMMARY

Introduction and Scope

Mention is made of the principle of the various methods for estimating the production of testis hormone.

It appears from publications on the subject that it will be possible to use the prostate as an organ recording the production of testis hormone in man and thus also the response of the testis to gonadotropin, because of the production of acid phosphatase by the gland, a production that has appeared to be an accessory male sex character.

The object of the present work has been to examine the production of phosphatase in the prostate in man in various conditions with a decreased output of testis hormone compared with a series of normal controls and in the course of various forms of treatment with hormones.

Chapter I

Historical Survey of Publications on Acid Prostate Phosphatase.

Prostate phosphatase was not detected in the urine until 1935. Ten years later the prostate was found to be the main source of acid phosphatase in male urine. The prostate proves to contain exorbitant amounts of acid phosphatase in man and in monkeys, but only after puberty. In prepubertal monkeys an output of the enzyme may, however, also be produced by means of testosterone. A few observations show that the production of phosphatase is an accessory male sex character. From metastases of carcinoma of the prostate the enzyme may pass into the blood. The content in the blood decreases after castration and after treatment with oestrogens. In 1946 it was demonstrated

that the natural substrate of phosphatase is phosphoryl choline in seminal fluid.

Chapter II

Secretion of the Prostate

The weight of the prostate remains constant from about the twentieth to about the sixtieth year. Histologically a secretory cycle can be differentiated in which the cells display apocrine secretion. As early as about the fortieth year presenile changes set on which resemble castration changes.

Chapter III

Biochemical Properties of Prostate Phosphatase.

Minute amounts of testosterone are capable of preventing the regression of the prostate in rats after castration, and testosterone can counteract the castration changes in the prostate completely.

Testosterone stimulates the aerobic carbohydrate metabolism of the prostate.

Testosterone influences the acini, whereas oestrogen chiefly exerts its effect on the fibromuscular elements and the epithelium of the excretory ducts, besides neutralizing the testosterone effect.

Hypophysectomy causes prostatic atrophy, which may be counteracted by gonadotropin.

The suprarenal glands promote the growth of the prostate, but only until about the fortieth day of life in infantile, castrated male rats.

Adrenocorticotropic hormone may produce prostatic hypertrophy in immature, castrated, but not adrenalectomized rats.

Desoxycorticosterone seems to be without any effect on the prostate.

The histological picture of the prostate of castrated animals is influenced by smaller doses of testosterone and oestrogen than those required to influence the vesicular glands.

Chapter IV

Normal Anatomy and Histology of the Prostate.

The canine prostate has a large daily volume of secretion; it is reduced in the course of inanition but may be increased

again under the same condition by means of treatment with androgens and gonadotropin. Further, it decreases after castration and in the course of treatment with oestrogen.

The secretion is governed by the nn. hypogastrici and erigentes and may be influenced by various drugs; pilocarpine exerts a particularly stimulating effect. The pressure of secretion is about 100 cm water-pressure. The male prostate produces only very slight quantities of secretion, apart from the ejaculates.

The prostatic secretion is characterized, *inter alia*, by its high content of calcium and citrate, lipoids, and — in man — acid phosphatase.

Chapter V

Influence of Hormones in the Prostatic Tissue.

Acid prostate phosphatase is a monophosphatase and chemically an amphoteric electrolyte with globulin properties. It has not been possible to distinguish an apo- and a co-enzyme.

With a constant ionic strength the pH activity has its optimum about 6.3 with regard to phosphoryl choline, and about 6.0 with regard to phenyl or glycerophosphate.

The pH-stability is greatest with pH between 4 and 6. The keeping qualities of the enzyme in seminal fluid are good. It is inhibited, among other substances, by fluoride, maleïnate, and oxalate, to some extent dependent on the presence of other substances, such as Mg^{++}, citrate and fluoride. It is irreversibly inactivated by alcohol, acetone and ether but remains uninfluenced by formaldehyde.

Chapter VI

Content of Acid Phosphatase in the Urine

In middle-aged men the phosphatasuria is from 4 to 5 times greater than in women. In children and in old individuals its size is independent of the sex.

The 24-hour excretion seems to show a good individual constancy, but varies much from one man to another. The share of the prostatic secretion in the 24 hours can be calculated to 0.05 ml on the average. In the course of treatment of a castrate with testosterone the concentration of phosphatase in the urine rose to three times the normal. Morning urine of normal men may contain especially large quantities of phosphatase.

Sexual stimulation and ejaculation do not cause regurgitation of phosphatase to the bladder or to the posterior urethra (writer's examinations).

Chapter VII

The Ejaculate in Man.

During an ejaculation the prostatic secretion is first ejaculated, then follows the secretion of the testes-epididymis-vas deferens, and finally the vesicular glands are evacuated, which can be demonstrated by determinations of the concentrations of phosphatase, spermatozoa and fructose in ejaculates collected by fractionation.

The separation of these secretions is not absolute, as the first fraction may contain a small proportion of fructose, and the last a little phosphatase. The examinations of all previous authors as well as the writer's examinations show that ejaculates with or without defective spermatozoa have the same concentration of phosphatase as those of normal individuals. But there is some difference of opinion with regard to the individual constancy of the concentration of the enzyme in the ejaculate.

In individuals with a low concentration in the ejaculate it is, however, found to be fairly constant from time to time.

In the writher's examinations the share of the prostatic secretion in the normal, human ejaculate averaged 27 per cent., a value which has also been found by previous authors.

The concentrations of proteins, citrate and spermatozoa in semen are decreasing in ejaculates following in rapid succession.

The concentration and the amount of phosphatase, on the other hand, are rather constant, except (writer's examinations) after intervals of few minutes between the ejaculations.

The volume of the ejaculation remains uninfluenced by testosterone but is reduced by oestrogen to about 0.50 ml after treatment for one or several months. In the course hereof the concentration of fructose displays a great fall, whereas that of phosphatase does not show any unquestionable tendency in either direction.

In prostatitis the fractionation of the prostatic ejaculation is suspended (writer's examinations) and the concentra-

tion of phosphatase in ejaculate and expressed secretion is lowered.

Chapter VIII

Previous Examinations of the Connection between hypandrogenic Conditions and the Presence of varying Substances (excluding Phosphatase) in the Ejaculate.

The content of proteins, citrate (from the prostate) and fructose (from the vesicular glands) in the ejaculate is reduced by castration, but increases again in the course of treatment with testosterone.

Chapter IX

Previous Examinations of the Production of Phosphatase in Hypandrogenic Conditions.

Only four previous publications on acid prostate phosphatase in man deal with the relation to the production of androgens. The extent to which the testis hormone is responsible for the production of phosphatase and the importance of other hormones of the organism have not been examined previously, nor has it been attempted yet on the basis of the phosphatase reaction in spontaneous puberty and in connection with treatment to elucidate the functional capacity of the testes and the pituitary during normal puberty and in hypandrogenic individuals.

Chapter X

Writer's Examinations of the Concentration of Phosphatase in expressed prostatic Secretion.

The concentration of phosphatase is determined by means of a modified Gutman and Gutman technique. For duplicate determinations a quantity of 20 mm^3 of expressed secretion is sufficient. The unit of the concentration of phosphatase is 1 K.P.U. (kilophosphatase-unit, implied per ml of secretion). which equals 1000 Gutman and units.

The error of determination on the mean figure of a duplicate test of mixed expressed secretion is <10 per cent. The error is somewhat greater when a duplicate test is made as a determination in the portion first expressed and in the one last ex-

pressed, presumably because af an actually different content of phosphatase in the two portions.

Any admixture of urine to the expressed secretion is demonstrated by means of precipation with picric acid, sedimentation and alkalinization of the supernatant liquid, followed by colorimetric determination (creatinine detection). The admixture is stated in per cent. Quantities from 10 to 50 mm^3 of expressed secretion are used for this test. The method affords a good quantitative estimate.

The admixture of vesicular secretion is detected by means of its content of fructose with a modified Jordan and Pryde method. Quantities from 10 to 20 mm^3 of expressed secretion are used for this test. The proportion of fructose is stated in gammas per 10 mm^3 of secretion. The method does not give more than a rough estimate of the admixture of secretion from the vesicular glands. It is shown that few expressed secretions contain this admixture which, as a rule, can be recognized already during the expression.

Ejaculates of hypandrogenic individuals display a greater variation of the concentration of fructose than of that of phosphatase. The results seem to indicate that the influence of testis hormones giving rise to a production of phosphatase does not differ much from the one causing a production of fructose. We may therefore conclude that the absence of a fructose reaction in expressed secretions from hypandrogenic individuals means that they contain no admixture of secretion from the vesicular glands.

The volume of the testes is calculated from the formula applying to the volume of an oblate ellipsoid after measuring the height, thickness and width, and deduction of the thickness of the reduplication of the scrotum.

The length and the transverse diameter are measured on the non erected penis.

The pubes are classified in seven groups according to the intensity. The growth of terminal hair is divided into five groups, according to the presence of pubes, axillary hair and beard, and the intensity of shaving. A deviation from the chronological sequence: pubes, hirci, barbae in the form of the development: pubes-barbae-hirci has been found in a few cases, but not the sequence: hirci-pubes.

An estimate of the prostate is obtained by rectal exploration, and the gland is classified in five groups according to size and consistency.

The expressed secretion is estimated according to its degree of cloudiness, and divided into four groups.

The renal excretion of gonadotropin, androgens and oestrogen is determined according to Pedersen-Bjergaard and Tønnesen (1948).

The age of development of the carpal bones has been fixed by comparison of roentgenograms with Todd's standard atlas (1937).

Chapter XI

Choice of a Criterion of the Production of Phosphatase in the Prostate.

The determination of the concentration, respectively amount, of phosphatase in the ejaculate will exclude markedly hypandrogenic patients suffering from aspermatism from examination, and the results even in patients from whom seminal fluid can be obtained are difficult to estimate.

It is shown that it is not possible to measure the output of phosphatase by the prostate per time unit. Consequently, another function must be chosen as a criterion of the secretory intensity of the prostate. It is considered objectionable to use the content of phosphatase in 24-hour urine as suggested by Scott and Huggins (1942). Instead hereof the concentration of phosphatase in expressed prostatic secretion has been used in the present work.

Chapter XII

Applicability of the Concentration of Phosphatase as an Indicator of the Production of Testis Hormone.

Whether the concentration of phosphatase in expressed secretion as an indication of the output of the enzyme by the prostate is an applicable criterion of the production of testis hormone, is a question which it is attempted to settle here by examining to what extent the concentration of phosphatase complies with certain demands. It seems as if it rises only under the influence of testosterone and chorionic gonadotropin, whereas no effect of equine gonadotropin, oestradiol and thyroid hormone has been demonstrated.

The pathologically increased production of adrenocortical hormone in adrenal pubertas præcox and intersex produces an extragonadal rise of the concentration of phosphatase.

The sensitivity of the production of phosphatase to testosterone varies very much from one man to another, and even with very high doses a normal concentration of phosphatase cannot always be provoked. The supposed causes hereof are discussed. Two possibilities are pointed out: the prostate may lack the power of producing a normal concentration of the enzyme, or the patients displaying a suboptimal response may lack a hormone augmenting the effect of the testis hormone. As chorionic gonadotropin appears not to increase the concentration of phosphatase above the level which can be obtained by means of testosterone, and as equine gonadotropin exerts no effect, it is improbable that the — hypothetic — hormone is derived from the testes. A certain phosphatase reaction was produced in all the patients treated except one, a castrate in the senium.

It was found in a eunuchoid that 5 mg of methyl testosterone daily took the concentration of phosphatase into the normal range, and 20 mg daily only caused a slight additional increase.

In a number of individuals no small variations of the concentration of phosphatase are found from one expressed secretion to another. The causes hereof are examined. The variations cannot be explained solely by technically wrong analyses or by admixtures to the prostatic secretion in the course of the expression. In fractionated collection of expressed secretion unsystematical variations of the concentration of phosphatase are found in the same expressed secretion. It is discussed whether the cause hereof is an admixture of phosphatase-free secretion from the areas in the prostate termed "negative" according to Gomori.

It is possible that the variations occurring in expressed secretions from the same individual are due to a changing output of testis hormone. The fact that the androgenuria varies much from day to day, speaks in favour hereof.

The present investigations of the concentration of phosphatase after instituted and after discontinued treatment with testosterone show that the latent period rarely exceeds 1½ months, and that a stationary condition is soon established in the course of treatment (a few weeks after commencement of the production of phosphatase).

The time passing from discontinuance of the treatment to the onset of the fall is of the same magnitude as the latent period, the total period of abatement, however, shows a greater variation

In treatment with chorionic gonadotropin the same periods are found; however, in a few patients, latent periods are found up to 3 months. Prolonged latent periods are seen in particular when there is no initial production of phosphatase.

Repeated treatment after a brief interval results in a shortened latent period.

The period of abatement remains uninfluenced by the initial production of phosphatase.

It is stressed that in the course of treatment with chorionic gonadotropin the periods mentioned can only with reservation be compared with the similar periods in the course of testosterone therapy, as the time of response of the testes, and a constant production of testis hormone that may possibly have been started, may convey a wrong impression of the latent period and the period of abatement of the prostate.

It is concluded that an actual concentration of phosphatase is indicative of the production of testis hormone present from 1 to 2 months in advance.

Chapter XIII

Series of normal Cases.

In 33 middle-aged men the concentration of phosphatase in the first expressed secretion varied from 4.0 to 21.3 K.P.U. The mean figure is about 10 K.P.U., and the lower limit of the normal is fixed at 5 K.P.U.

Among 13 individuals under the twentieth year and 12 over the sixtieth year completely normal as well as reduced values were found. The dependence of the values on the year of life very much resembles the relation to age ascertained by Hamburger (1948) in the case of androgenuria and the testogenic 17-ketosteroid excretion, even though the maximum concentration of phosphatase appears a decade earlier, namely in the third decade, when the maximum of the excretion of 17-ketosteroids originating from testes + suprarenal glands also appears.

Chapter XIV

Hypandry and sexual Maturity. Nosographic Considerations.

The term hypandry is chosen by way of definition of the condition in which the somatic accessory sex characters have not reached complete development. By physiological hypandry is understood a virile development less than that of normal adult men, in pathological hypandry the development is less than the one normal for the age.

The difficulties in diagnosing a pathological hypandry in boys under 16 years are stressed, and it is discussed whether there exists any significant production of androgens at all during the first decade.

The various groups of disorders which are related to sexual maturation are described and defined.

Infantilism is defined in the present work as a form of inhibited development in which the somatic and psychical development correspond in several respects to a younger age than that of the patient. When the patient has passed the age of normal sexual maturation, the presence of a pathological hypandry will moreover be required to establish the diagnosis. In contrast with the definitions given by other authors, the term is used in the present work also in the case of children, irrespective of the fact whether a pathological hypandry can be demonstrated, but then only in cases in which experience shows that puberty is likely to begin late and to be slow or defective, i. e. at the age when it can be ascertained that these patients will often appear to be hypandronic. By means of this reservation cases of nanism caused by elective injury of the osseous system are excluded.

Infantilism is divided into primary, i.e. cryptogenetic, and secondary infantilism (following some established disorder). The term hypophyseal infantilism has not been employed in the present book.

Pubertas tarda s e n s u s t r i c t i o r i is suggested as a proper term for a number of cases occurring in part of these series in whom the predominant feature is late or defective puberty, whereas there were no or only slight symptoms of infantilism during childhood.

The term eunuchoid has been used in the case of (pathologically) hypandrogenic adults with eunuchoid proportions.

The literature dealing with the so-called adiposogenital dystrophy is gone over. It is stressed that pathological hypandry is rarely included in the syndrome adiposogenital dystrophy.

Finally, two groups are defined: sexually mature dwarfs and hypoplasia testis.

Chapter XV

Writer's Examinations of the Correlation between the Concentration of Phosphatase and the other Somatic Sex Characters in Hypandry and certain other Conditions.

The series consists of 166 men under 60 years, partly physiologically or pathologically hypandrogenic individuals (adiposogenital dystrophy, infantilism, pubertas tarda, eunuchoidism) and partly men without any somatic hypandry, suffering from impotentia coeundi, hypoplasia testis and gynaecomastia.

The concentration of phosphatase in the expressed secretion first examined has been compared to the development of the various accessory sex characters.

There is only a slight relation to the volume of the testes. Even very small testes may be accompanied by a normal concentration of phosphatase and, conversely, a normal volume does not preclude a lowered production of the enzyme.

A testicular volume of 10 ml (the lower limit of the total testicular volume in normal, middle-aged men) appears earlier during puberty than a normal concentration of phosphatase ($\geqq$5 K.P.U.).

The length and diameter of the penis increase with a rising concentration of phosphatase, and the pubes and the remaining growth of terminal hair and the size of the prostate also increase.

The appearance of the prostatic secretion follows the concentration of phosphatase. All stages are seen, from watery to milky appearance. In the individual hypandrogenic patients this metamorphosis can be observed in the course of treatment with chorionic gonadotropin.

The concentration of phosphatase becomes normal earlier in puberty than the androgenuria.

A development of the carpal bones less than the one normally observed from the thirteenth to the fourteenth year of life is very rarely accompanied by a production of phosphatase, let alone a normal concentration of the enzyme.

The correlation between the concentration of phosphatase and the other somatic sex characters examined seems largely to be independent of whether the patients have been left untreated or have been previously treated with sex hormones.

A normal concentration of phosphatase occurs in some normal boys as early as from the thirteenth year of life.

It is shown that the production of phosphatase in patients suffering from infantilismus primarius et secundarius, pubertas tarda and eunuchoidism may appear spontaneously, though it may be delayed a few years.

In hypoplasia testis with otherwise virile sex characters a normal concentration of phosphatase is found; however, in a few cases signs of a slight decrease of the production of testis hormone are observed.

It is moreover shown that a spontaneously established normal concentration of phosphatase does not preclude a (moderately) decreased output of testis hormone.

Twenty-two patients suffering from impotentia coeundi displayed a normal concentration of phosphatase except for one whose production of phosphatase remained uninfluenced by treatment with chorionic gonadotropin.

Gynaecomastia is accompanied by a production of phosphatase corresponding to the development of the accessory sex characters (4 cases).

Chapter XVI

Sexual Maturation and its Mechanism in Boys. Previous Investigations.

The somatic stigmata of prepuberty and puberty are described, and it appears that the first signs of increased gonadotropin and sexual activity can be noticed at the end of the first decade and at the beginning of the second. Special mention is made of the volume of the testes, the lower normal limit of which before the thirteenth year of life must apparently by fixed as low as at 1 ml. Deviations from normal puberty are briefly described.

In the present work, puberty is defined as the period from the appearance of the first pubes until sexual maturation has

been completed, provided that this sexual maturation is due to a spontaneously lasting production of testis hormone.

The sex character produced by testosterone preparations is therefore not a puberty.

In the course of treatment with gonadotropin two fundamentally different conditions may be produced: a puberty which, once started in this way, is maintained after discontinuance of the treatment (termed provoked puberty), or a sexual maturation caused by the production of testis hormone which is only maintained in the course of treatment and ceases later (termed imitation of puberty).

It seems as if no distinction has been made so far between these two prognostically important forms, possibly because the criteria employed for the production of testis hormone are highly irreversible. It is supposed that treatment of normal boys with chorionic gonadotropin will lead to provoked puberty in prepuberty, whilst treatment during the first years of life is more likely to produce an imitation of puberty, thus not a pubertas præcox.

Chapter XVII

Writer's Examinations of the Different Forms of Puberty by Means of the Phosphatase Reaction.

It proves possible by means of the phosphatase reaction to distinguish clearly between the two forms of sexual maturation, provoked puberty and imitation of puberty, and it has also become possible to ascertain when a provoked but subtotal puberty may be replaced by a spontaneous puberty later in the course. In untreated individuals it appears that spontaneous puberty causes a very slow rise of the concentration of phosphatase (from months to years), whereas treatment with chorionic gonadotropin may produce a very rapid rise (from weeks to a few months).

If the concentration of phosphatase is followed during a series of injections of chorionic gonadotropin the following points can be illustrated: the spontaneous production of testis hormone, the functional "readiness" of the testes and the prostate, the maximum power of the testis to produce hormones, respectively the faculty of the prostate for a production of phosphatase, and the power of the testes to continue the production of hormone

once they have been stimulated. Finally, the course permits certain conclusions as to the mutual relation between the pituitary and the testes. Almost all hypandrogenic patients in puberty who have been examined responded with a production of testis hormone during the first series (1500 I.U. of Physex Leo × about 30 for about 3 months), but a normal production of phosphatase is only obtained in a minority of the patients.

It is shown that the cause of the failing production of phosphatase cannot be attributed to too low a dose.

After discontinuance of the treatment the production of testis hormone continues in some cases (provoked puberty) and ceases again in others (imitation of puberty).

In the course of treatment with one series of chorionic gonadotropin in 19 previously untreated hypandrogenic patients with primarily lacking production of phosphatase (2 of whom did not respond) it is shown that all the 6 patients suffering from adiposogenital dystrophy respond with provoked puberty, whilst 8 out of the 11 patients of the infantilism group (i.e. infantilismus, pubertas tarda, eunuchoidismus) only attained an imitation of puberty. The difference cannot be explained by any dissimilarity between the two groups of patients with regard to age, volume of the testes, intensity of treatment, or period of observation.

The explanations of the fact that it is altogether possible to achieve a provoked puberty are referred to in detail. It is supposed that in patients suffering from adiposogenital dystrophy the pituitary produces a sufficient quantity of gonadotropin to maintain a testicular function which has been started by the administration of hormone. The 4 out of the 6 suffering from this disorder showed a pituitary function which could not have been better in normal boys.

Based on the literature on the subject the conclusion is drawn from the phosphatase reaction in adiposogenital dystrophy that these patients can hardly be considered pathologically hypandrogenic, and that their pituitary function is — at any rate potentially — normal.

As the phosphatase reaction of normal boys to treatment with chorionic gonadotropin has not been examined in the present work, it is still an open question whether the often subnormal phosphatase reaction is indicative of a poor function of the tes-

tes, or whether it is physiological just at that age. The patients suffering from adiposogenital dystrophy cannot, however, suffer from any great defect of the testes, since the production of hormone continues after treatment.

The provoked, subnormal production of phosphatase is often, after the course of months or years, replaced by a spontaneous rise to normal values, presumably indicative of a spontaneously increased production of testis hormone.

A treatment of patients of the infantilism group with repeated series of chorionic gonadotropin will most frequently reduce the latent period and improve the preliminary production of phosphatase; but a provoked puberty was caused by repeated treatment only in 2 out of 7 in whom the response to the first series was an imitation of puberty. In a number of patients a spontaneous rise of the concentration of phosphatase is observed long after the treatment has been discontinued. This rise is found to be indicative of an intensification of the processes of puberty, which would possibly have occurred even if the precious treatment had not been instituted.

A survey is given of the combinations of imitations of puberty, spontaneous and provoked puberty, which occur in all the hypandrogenic patients (total 36) treated with chorionic gonadotropin. It is shown that an imitation is followed by a provoked or spontaneous puberty in one-third of the cases or so. The age seems here to be of decisive importance. If the patient is over 20 years, the chances that the imitation will be replaced by puberty are very small.

A provoked subtotal puberty seems to be replaced by a subsequent superimposed spontaneous puberty more frequently among patients suffering from adiposogenital dystrophy than in the infantilism group. In many of the patients the provoked puberty produced by treatment with chorionic gonadotropin is presumably just an anticipation of the production of testis hormone which would have occurred spontaneously later on.

Chapter XVIII

Relation between Type of Puberty and Degree of Sexual Maturity attained

Owing to its unequal composition the series of cases is less suited for a comparison between the degree of sexual maturity

It is, however, demonstrated that the sexual maturity which is produced by a total (provoked or spontaneous) puberty is greater than in the case of imitation, with which it is difficult, in spite of intensive treatment, to obtain a normal volume of the testes and a growth of terminal hair corresponding to the patient's age. As already mentioned, it is difficult, without using the phosphatase reaction, to diagnose the nature of the response of the urine in connection with a series of injections of chorionic is great that, in spite of intensive treatment, only an imitation of puberty is attained when the patient treated belongs to the infantilism group, is over 20 years and has small testes.

Lastly, it is found that spontaneous puberty occurs earlier in the patients suffering from adiposogenital dystrophy than in those of the infantilism group.

Chapter XIX

Influence of Chorionic Gonadotropin Treatment on the Phosphatase Concentration and on the Excretion in Urine of Gonadotropic, Androgenic and Oestrogenic Substances.

Six patients were followed by means of hormone analyses of the urine in connection with a series of injections of chorionic gonadotropin. The rise of the androgenuria is found to be a less sensitive, that of the oestrogenuria an equally or more sensitive criterion of the stimulation of the testis than the rise of the concentration of phosphatase. Strangely enough the production of phosphatase (i.e. the production of testis hormone) may improve permanently, whilst at the same time the increase of the renal excretion of gonadotropin, androgen or oestrogen is transient.

Chapter XX

Lines of Treatment of Hypandrogenic Individuals with Chorionic Gonadotropin based on the Phosphatase Reaction.

It is shown by means of the phosphatase reaction that hypergonadotropinuria neither excludes imitation of puberty nor provoked puberty. The explanation is presumably that the treatment with chorionic gonadotropin in the doses employed is a far more vigorous stimulant for the testes than even an increased production of pituitary gonadotropin. Conversely, a

normal gonadotropinuria does not exclude that only an imitation of puberty is produced. It is supposed that hypergonadotropinuria is too sensitive a criterion of the state of the testes to be of decisive prognostic importance.

The clinical improvement in markedly hypandrogenic patients of the first series of treatment is much about the same from one patient to another and, therefore, not suitable as the basis of a differentiation of the response of the testes to the treatment.

On the other hand the phosphatase reaction may be used to distinguish whether the first series results in a temporary or a permanently increased production of testis hormone, and thus — though with a certain reservation (see Chapter XVII) — to form an estimate of the effect of subsequent series af chorionic gonadotropin.

The prognosis of the further spontaneous course should also be estimated with a certain reservation on the basis of the phosphatase reaction, as an imitation of puberty or a provoked subtotal puberty may later be replaced by a spontaneous puberty (see Chapter XVII).

In conclusion the main lines of treatment with chorionic gonadotropin are discussed.

In most cases of adiposogenital dystrophy it will be rational to omit any treatment with hormones, the only effect of which will as a rule be to accelerate a puberty which would otherwise have occurred at the normal time. When, as a rare exception, the spontaneous puberty has not commenced about the fifteenth or sixteenth year, treatment is indicated.

Although treatment of patients belonging to the infantilism group is much better indicated also before the sixteenth year because of the often failing, late or defective spontaneous puberty, it may be pointed out that chorionic gonadotropin will often produce only an imitation of puberty and in such cases is not more effective than testosterone.

Besides giving the patient a chance of provoked puberty a treatment with chorionic gonadotropin instituted in good time will most frequently cause an acceleration of the growth and of the maturation of the epiphyses, so that the occurrence of eunuchoid proportions is prevented or counteracted.

RESUMÉ

Indledning og problemstilling.

Princippet i de forskellige metoder til vurdering af testishormonproduktionen omtales.

Foreliggende arbejder tyder på, at prostata vil kunne anvendes som registreringsorgan for individets egen testishormonproduktion og derved også for testes' reaktion på tilført gonadotropin takket være kirtlens produktion af sur fosfatase, der har vist sig at være en accessorisk, mandlig kønskarakter.

Dette arbejdes mål har været at undersøge fosfataseproduktionen i prostata hos manden ved forskellige tilstande med nedsat testishormonproduktion sidestillet med et normalt kontrolmateriale og under forskellige hormonbehandlinger.

Kapitel I. Historisk oversigt over arbejder vedrørende den sure prostatafosfatase.

Prostatafosfatasen opdagedes først i urinen i 1935. 10 år senere fandtes prostata at være hovedkilden til sur fosfatase i mandsurin. Prostata viser sig at indeholde exorbitante mængder af sur fosfatase hos mænd og aber, men kun efter puberteten. Produktionen kan dog også fremkaldes hos aber i præpuberteten med testosteron. Enkelte iagttagelser viser, at fosfataseproduktionen er en accessorisk, mandlig kønskarakter. Fra prostatacarcinommetastaser findes fosfatasen at gå over i blodet. Indholdet her aftager efter kastration og østrogenbehandling. I 1946 påvistes det, at fosfatasens naturlige substrat er fosforylcholin i sperma.

Kapitel II. Prostatas normale anatomi og histologi.

Prostatavægten er konstant fra omkring 20. til omkring 60. år.

Histologisk kan uddifferentieres en sekretionscyclus, i hvilken cellerne har apokrin sekretion. Allerede fra 40. år sætter præsenile forandringer ind, der ligner kastrationsforandringer.

Kapitel III. Hormonernes indvirkning på prostatavævet.

Meget små testosteronmængder formår at hindre regressionen af prostata hos rotter efter kastration, og testosteron kan fuldt ud ophæve kastrationsforandringerne i prostata.

Testosteron stimulerer prostatas aerobe kulhydratstofskifte.

Mens testosteron påvirker endestykkerne, virker østrogen overvejende på de fibromuskulære elementer og på epithelet i udførselsgangene, foruden at det neutraliserer testosteronvirkningen.

Hypofysectomi medfører prostataatrofi, der modvirkes af gonadotropin.

Binyrerne stimulerer prostatavæksten dog kun indtil omkring 40. levedag hos infantile, kastrerede hanrotter.

Med adrenocorticotropt hormon kan fremkaldes prostatahypertrofi hos immature, kastrerede, men ikke adrenalectomerede rotter.

Desoxycorticosteron synes uden virkning på prostata.

Det histologiske billede i prostata fra kastrerede dyr påvirkes af mindre doser testosteron og østrogen end nødvendigt til påvirkning af glandulae vesiculares.

Kapitel IV. Prostatas sekretion og prostatasekretet.

Hundens prostata har stort daglig sekretionsvolumen; det mindskes under inanition, men kan herunder atter øges med androgen- og gonadotropinbehandling. Det aftager ligeledes efter kastration og under østrogenbehandling.

Sekretionen står under indflydelse af nn. hypogastrici og erigentes og kan påvirkes af forskellige pharmaca, især virker pilocarpin forøgende. Sekretionstrykket er omkring 100 cm vand. Den mandlige prostata producerer kun ubetydelige sekretmængder, bortset fra ejakulaterne.

Prostatasekretet karakteriseres blandt andet ved stort indhold af calcium og citrat, lipoider og — hos mennesket — sur fosfatase.

Kapitel V. Prostatafosfatasens biokemiske egenskaber.

Den sure prostatafosfatase er en monofosfatase og kemisk en amfolyt med globulinegenskaber. Adskillelse i apo- og coenzym er ikke lykkedes.

Med konstant jonstyrke er pH aktivitetsoptimum fundet til omkring 6.3 over for fosforylcholin og omkring 6.0 over for fenyl- eller glycerofosfat.

pH-stabiliteten er størst mellem pH 4 og 6. Holdbarheden i sperma er stor. Enzymet hæmmes blandt andet af fluorid, maleïnat, oxalat, noget afhængigt af andre stoffers tilstedeværelse som Mg^{++}, citrat og fluorid. Det inaktiveres irreversibelt af alkohol, acetone og æther, men påvirkes ikke af formaldehyd.

Kapitel VI. Urinens indhold af sur fosfatase.

Hos midaldrende mænd er fosfatasurien 4—5 gange større end hos kvinder. Hos børn og gamle er dens størrelse uafhængig af kønnet.

Døgnudskillelsen synes at vise god individuel konstans, men varierer meget fra mand til mand. Prostatasekretets andel pr. døgn kan beregnes til gennemsnitlig 0.05 ml.. Under testosteronbehandling af en kastrat fandt man i urinen fosfatasekoncentrationen steget til det 3-dobbelte. Morgenurinen fra normale mænd kan indeholde særligt store fosfatasemængder.

Seksuel stimulation og ejakulation giver ikke regurgitation af fosfatase til blæren eller urethra posterior (egne undersøgelser).

Kapitel VII. Ejakulatet hos manden.

Under en ejakulation ejakuleres først prostatasekretet, derefter testes-epididymis-ductus deferens sekretet, og til slut tømmes glandulae vesiculares, hvilket kan vises ved bestemmelse af fosfatase-, spermie- og fruktosekoncentrationen i fraktioneret opsamlet ejakulat.

Adskillelsen af disse sekreter er ikke absolut, i første fraktion findes lidt fruktose, og i sidste lidt fosfatase. Samtlige tidligere forfatteres og egne undersøgelser viser, at ejakulater uden eller med defekte spermier har samme fosfatasekoncentration som normale ejakulater. Derimod hersker uenighed om den individuelle konstans med hensyn til fosfatasekoncentrationen i ejakulatet.

Hos individer med lav koncentration i ejakulatet findes dog god konstans fra gang til gang.

Ved egne undersøgelser findes prostatasekretets andel i det normale, humane ejakulat til gennemsnitlig 27 %, en størrelsesorden, der også findes af tidligere forfattere.

Proteinstof-, citrat- og spermiekoncentrationen i sperma er faldende i kort på hinanden følgende ejakulater.

Fosfatasekoncentrationen og -mængden er derimod fundet ret konstant, undtagen (egne undersøgelser) efter kun få minutters ejakulationspause.

Testosteron påvirker ikke ejakulationsvolumen, mens østrogen nedsætter det til omkring ½ ml efter een til flere måneders behandlingstid. Fruktosekoncentrationen falder herunder stærkt, mens fosfatasekoncentrationen ikke viser sikker tendens i nogen retning.

Ved prostatitis kan findes ophævet fraktionering af prostataejakulationen (egne undersøgelser) og nedsat fosfatasekoncentration i ejakulat og eksprimat.

Kapitel VIII. Tidligere forfatteres undersøgelser over sammenhængen mellem hypogonade tilstande og tilstedeværelsen af forskellige stoffer (ikke fosfatase) i ejakulatet.

Ejakulatets indhold af proteinstof, citrat fra prostata og fruktose (fra glandulae vesiculares) mindskes ved kastration, men øges atter under testosteronbehandling.

Kapitel IX. Tidligere forfatteres undersøgelser over fosfataseproduktionen ved hypandri.

Kun 4 tidligere arbejder over den sure prostatafosfatase hos manden omhandler relationen til den androgene produktion. Det er tidligere ikke undersøgt, i hvilket omfang testishormonet er ansvarlig for fosfataseproduktionen, og hvilken betydning organismens andre hormoner har, ligesom man endnu ikke har forsøgt ud fra fosfatasereaktionen i den spontane pubertet og i tilslutning til behandling at få oplysning om testes' og hypofysens funktionsdygtighed i den normale pubertet og hos hypandrine.

Kapitel X. Egne undersøgelser over fosfatasekoncentrationen i prostataeksprimat.

Fosfatasekoncentrationen bestemmes med modificeret Gut-

man & Gutman-teknik. Til dobbeltprøver er 20 mm^3 eksprimat tilstrækkeligt. Som enhed for fosfatasekoncentrationen anvendes K. P. U. (= Kilophosphatase Unit, underforstaaet pr. ml sekret), som er lig 1000 Gutman & Gutman-enheder.

Målefejlen på middeltallet af en dobbeltprøve af blandet eksprimat findes at være < 10 %. Fejlen er noget større, når en dobbeltprøve udføres som en bestemmelse på det først eksprimerede og på det sidst eksprimerede, antagelig på grund af et faktisk forskelligt fosfataseindhold i de to portioner.

Eventuel urintilblanding i eksprimatet påvises med pikrinsyrefældning, sedimentering og alkalisering af og kolorimetri på den ovenstående vædske (kreatininpåvisning). Tilblandingen opgives i procent. Der anvendes hertil 10—50 mm^3 eksprimat. Metoden findes at give et godt kvantitativt skøn.

Tilblandingen af vesiculærsekretet påvises gennem dets fruktoseindhold med en modificeret Jordan & Pryde-metode. Hertil anvendes 10—20 mm^3 eksprimat. Fruktosemængden opgives i gamma pr. 10 mm^3 sekret. Mere end et groft skøn over tilblandingen af glandulae vesiculares sekret giver metoden ikke. Det pavises, at kun få eksprimater indeholder dette sekret, og at tilblandingen som regel kan erkendes allerede under ekspressionen.

I ejakulater fra hypandrine findes større variation i fruktose- end i fosfatasekoncentrationen. Resultaterne taler for, at der ikke er større forskel på den testishormonpåvirkning, der fremkalder fosfataseproduktion og den, der fremkalder fruktoseproduktion. Det er derfor tilladeligt at slutte fra manglende fruktosereaktion i eksprimater fra hypandrine til manglende versiculærsekret tilblanding.

Testesvolumen beregnes efter formlen for en omdrejningsellipsoides volumen efter måling af højde, tykkelse og bredde og fradrag af scrotumduplikaturens tykkelse.

På ikke erigeret penis måles længde og tværdiameter.

Pubesbehåringen inddeles i 7 klasser efter intensitet. Terminalbehåringen i 5, efter om der er pubes, hirci og barbae og barberingens intensitet. Afvigelse fra den kronologiske rækkefølge: pubes, hirci, barbae i form af udviklingen: pubes-barbae-hirci er fundet enkelte gange, derimod ikke: hirci-pubes.

Prostata vurderes ved rektal eksploration og inddeles i 5 klasser efter størrelse og konsistens.

Eksprimatet vurderes efter graden af skyethed i 4 klasser.

Den renale hormonudskillelse af gonadotropin, androgen og østrogen bestemmes efter Pedersen-Bjergaard & Tønnesen (1948).

For håndrodsknoglerne er ansat en udviklingsalder ved sammenligning af røntgenfoto med Todd's standardatlas (1937).

Kapitel XI. Valg af kriterium for fosfataseproduktionen i prostata.

Bestemmelsen af fosfatasekoncentration henholdsvis -mængde i ejakulatet vil udelukke stærkere hypandrine med aspermatisme fra undersøgelse, og resultaterne hos patienter hvorfra sperma kan erhverves er vanskelige at bedømme.

Det vises, at det ikke er muligt at måle prostatas fosfataseproduktion per tidsenhed. Som kriterium for prostatas sekretionsintensitet må derfor vælges en anden funktion. Det findes betænkeligt at anvende døgnurinens fosfataseindhold som foreslået af Scott & Huggins (1942). I stedet er i dette arbejde principalt anvendt fosfatasekoncentrationen i prostataeksprimat.

Kapitel XII. Fosfatasekoncentrationens egnethed som indikator for testishormonproduktionen.

Om fosfatasekoncentrationen i eksprimatet som udtryk for fosfataseproduktionen i prostata er et anvendeligt kriterium for testishormonproduktionen søges her afgjort ved, at det undersøges, i hvilket omfang fosfatasekoncentrationen opfylder visse opstillede krav.

Det viser sig, at fosfatasekoncentrationen stiger under testosteron- og choriongonadotropinpåvirkning, mens det ikke er lykkedes at påvise virkning af serumgonadotropin, østradiol og thyreoideahormon.

Den patologisk forøgede binyrebarkhormonproduktion, ved adrenal pubertas præcox og intersex fremkalder en ekstragonadogen stigning i fosfatasekoncentrationen.

Der findes en overordentlig stor variation fra mand til mand i fosfataseproduktionens følsomhed over for testosteron, og selv med intens dosering lykkes det ikke altid at provokere normal fosfatasekoncentration. De formodede årsager hertil diskuteres. To muligheder fremhæves: prostata mangler evnen til at fremkalde normal fosfatasekoncentration, eller de suboptimalt reagerende patienter mangler et testishormonvirkningen augmente-

rende hormon. Da choriongonadotropin viser sig ikke at øge fosfatasekoncentrationen over det niveau, som opnaas med testosteron, og da serumgonadotropin er uden virkning, er det usandsynligt, at det — hypotetiske — hormon har sin oprindelse fra testes. En vis fosfatasereaktion fremkaldtes hos alle de behandlede undtagen een, en kastrat i seniet.

Hos en eunuchoid fandtes, at 5 mg metyltestosteron daglig bragte fosfatasekoncentrationen op i normalområdet og 20 mg daglig øgede kun niveauet ubetydeligt yderligere.

Der findes hos en del individer ikke ubetydelige variationer i fosfatasekoncentrationen fra eksprimat til eksprimat. Årsagerne hertil undersøges. Variationerne kan ikke forklares alene ved tekniske fejlanalyser eller tilblanding til prostatasekretet under ekspressionen. Ved fraktioneret opsamling af eksprimat findes usystematiske variationer i fosfatasekoncentrationen inden for samme eksprimat. Det diskuteres, om årsagen hertil er tilblanding af fosfatasefrit sekret fra de efter Gomori benævnte „negative" glandelafsnit i prostata.

Det er muligt, at variationerne fra eksprimat til eksprimat hos samme individ skyldes skiftende testishormonproduktion. Herfor taler, at androgenuriens størrelse varierer stærkt fra dag til dag.

Undersøgelser over fosfatasekoncentrationen efter påbegyndt og efter afsluttet testosteronbehandling viser, at latenstiden sjældent overskrider 1½ måned, og at stationær tilstand under behandlingen hurtigt opnås (få uger efter at fosfataseproduktionen er begyndt).

Tiden fra behandlingens seponering og indtil faldet begynder er af samme størrelsesorden som latenstiden, den totale afklingningstid viser dog større spredning.

Med choriongonadotropinbehandling findes de samme terminer; hos enkelte findes dog latenstider op til 3 måneder. Lange latenstider ses især, hvor initial fosfataseproduktion mangler.

Gentagen behandling efter kort tids pause giver forkortet latenstid.

Den initiale fosfataseproduktion er uden indflydelse på afklingningstiden.

Det fremhæves, at terminerne under choriongonadotropinbehandling kun med reservation kan sammenlignes med terminerne under testosteronbehandling, da testes' reaktionstid og

en eventuelt igangsat stadig testishormonproduktion vil kunne fortegne tiderne for prostatas latens- og afklingningstid.

Der konkluderes, at en aktuel fosfatasekoncentration er udtryk for den testishormonproduktion, der var tilstede 1—2 måneder i forvejen.

Kapitel XIII. Normalmaterialet. Fosfatasekoncentrationen i eksprimatet fra normale drenge og mænd.

Hos 33 midaldrende mænd fandtes fosfatasekoncentrationen i 1. eksprimat at variere mellem 4.0 og 21.3 K. P. U. Middeltallet ligger ved 10 K. P. U., og det normales nedre grænse sættes til 5 K. P. U.

Blandt 13 under 20. og 12 over 60. år findes såvel fuldt normale som nedsatte værdier. Værdiernes afhængighed af levealderen er meget lig den af Hamburger (1948) for androgenurien og den testogene 17-ketosteroidudskillelse fundne relation til levealderen, omend maksimum for fosfatasekoncentrationen ligger et tiår tidligere, nemlig i 3. decennium, hvor også maksimum ligger for den 17-ketosteroidudskillelse, der hidrører fra testes + binyrer.

Kapitel XIV. Hypandri og kønsmodning. Nosografiske overvejelser.

Betegnelsen hypandri vælges definitionsmæssig for den tilstand, hvor de somatiske, accessoriske kønskarakterer ikke har nået fuld udvikling. Ved fysiologisk hypandri forstås en viril udvikling mindre end hos normale voksne mænd, ved patologisk hypandri er udviklingen mindre end den for alderen normale.

Vanskelighederne ved at diagnosticere en patologisk hypandri hos drenge under 16 år fremhæves, og det diskuteres, om der overhovedet eksisterer en betydende androgenproduktion i det første decennium.

De forskellige sygdomsgrupper, der har relation til kønsmodningen, beskrives og afgrænses.

Infantilismus defineres i dette arbejde som en udviklingshæmning, hvor den somatiske og psykiske udvikling på flere områder svarer til et yngre alderstrin. Er patienten nået forbi alderen for normal kønsmodning, vil man til diagnosen desuden kræve tilstedeværelse af en patologisk hypandri. Betegnelsen benyttes i dette arbejde i modsætning til andre forfatteres de-

finition også over for børn, uanse tom en patologisk hypandri lader sig påvise, men reserveres da for tilfælde, der erfaringsmæssigt er udsat for at gå i sen, langsomt eller defekt pubertet, d. v. s., at de i den alder, hvor det kan konstateres, ofte vil vise sig at være hypandrine. Ved dette forbehold udelukkes nanismus forårsaget af elektive beskadigelser af knoglesystemet.

Infantilismus deles i primær i. e. kryptogenetisk og sekundær (efter kendt lidelse). Betegnelsen infantilismus hypofysaris er ikke anvendt i dette arbejde.

Pubertas tarda sensu strictiori foreslås som betegnelse for en del i materialet forekommende tilfælde, hos hvilke det dominerende er sen eller defekt pubertet, mens symptomerne på infantilisme i barneårene manglede eller var små.

Som eunuchoide er betegnet (patologisk) hypandrine voksne med eunuchoide proportioner.

Literaturen om den såkaldte dystrofia adiposo-genitalis gennemgås.

Det fremhæves at patologisk hypandri sjældent indgår i syndromet dystrofia adiposo-genitalis.

Endelig afgrænses to grupper: „kønsmodne, væksthæmmede" samt hypoplasia testis.

Kapitel XV. Patientmaterialet.

Materialet omfatter 166 mænd under 60 år, dels fysiologisk eller patologisk hypandrine (dystropia adiposogenitalis, infantilismus, pubertus tarda, eunuchoidismus), dels tilfælde uden somatisk hypandri som impotentia coeundi, hypoplasia testis og gynækomasti. Fosfatasekoncentrationen i 1. undersøgte eksprimat er sat i relation til forskellige accessoriske kønskarakterers udvikling.

Der findes kun ringe relation til testesvolumenet. Selv meget små testes kan være ledsaget af normal fosfatasekoncentration og omvendt udelukker normalt volumen ikke en nedsat fosfataseproduktion.

Et testesvolumen på 10 ml (den nedre grænse for normale, midaldrende mænds totale testesvolumen) nås tidligere i puberteten end normal fosfatasekoncentration ($\geqq$ 5 K. P. U.).

Penis' længde og diameter tiltager med stigende fosfatasekoncentration, ligeså øges pubes og den øvrige terminalbehåring samt prostatas størrelse.

Prostatasekretets udseende følger fosfatasekoncentrationen. Alle stadier ses fra vandigt til mælket udseende. Hos den enkelte hypandrine patient kan denne metamorfose ses under chorion-gonadotropinbehandling.

Fosfatasekoncentrationen bliver normal tidligere i puberteten end androgenurien.

En håndrodsudvikling, der er mindre end svarende til 13.—14. leveår er yderst sjældent ledsaget af fosfataseproduktion endsige normal fosfatasekoncentration.

Korrelationen mellem fosfatasekoncentrationen og de øvrige undersøgte somatiske kønskarakterer synes i det store og hele uafhængig af, om patienterne er ubehandlede eller tidligere har været kønshormonbehandlede.

Normal fosfatasekoncentration optræder hos nogle normale drenge allerede fra 13. leveår.

Det vises, at fosfataseproduktionen hos patienter med infantilismus primarius et secundarius, pubertas tarda og eunuchoidismus spontant kan sætte ind omend med nogle års forsinkelse.

Ved hypoplasia testis med iøvrigt virilt kønspræg findes normal fosfatasekoncentration, hos enkelte ses imidlertid tegn på en let nedsættelse af testishormonproduktionen.

Endvidere vises, at en spontant opnået normal fosfatasekoncentration ikke udelukker en (moderat) nedsat testishormonproduktion.

22 patienter med impotentia coeundi viser normal fosfatasekoncentration bortset fra en enkelt, på hvis fosfataseproduktion choriongonadotropinbehandling var uden effekt.

Gynækomasti ledsages af en fosfataseproduktion, der svarer til udviklingen af de accessoriske kønspræg (4 tilfælde).

Kapitel XVI. Kønsmodningen og dens mekanisme hos drengen. Tidligere undersøgelser.

Præpubertetens somatiske stigmata gennemgås, og det fremgår, at de første tegn på øget gonadotropin- og kønsaktivitet kan spores i slutningen af 1. decennium og begyndelsen af 2.. Omtale gives særligt testes' volumen, hvis nedre, normale grænse før det 13. leveår øjensynligt skal sættes så lavt som til 1 ml. Deviationer fra den normale pubertet beskrives kort.

Ved pubertet forstas i dette arbejde perioden fra de første pubes vokser frem og indtil kønsmodningen er komplet, forudsat, at denne kønsmodning skyldes en spontant vedvarende testishormonproduktion.

Det af testosteronpræparaterne fremkaldte kønspræg er derfor ikke en pubertet.

Under gonadotropinbehandling kan fremkaldes 2 principielt forskellige tilstande: en pubertet, der således startet vedligeholdes efter behandlingens ophør (benævnes her: provokeret pubertet) eller en kønsmodning forårsaget af en testishormonproduktion, der kun opretholdes under behandlingen og siden ophører (benævnes her: pubertetsimitation).

Der synes hidtil ikke at være skelnet mellem disse to prognostisk vigtige former, muligt fordi de anvendte kriterier på testishormonproduktionen er vidtgående irreversible. Der antages, at choriongonadotropinbehandling af normale drenge medfører provokeret pubertet i præpuberteten, mens behandling i de første leveår snarest synes at ville fremkalde en pubertetsimitation, altså ikke en pubertas præcox.

Kapitel XVII. Egne undersøgelser over de forskellige kønsmodningsformer ved hjælp af fosfatasereaktionen.

Med fosfatasereaktionen viser det sig muligt at sondre klart imellem de to kønsmodningsformer, provokeret pubertet og pubertetsimitation, ligesom man er blevet i stand til at konstatere, når en provokeret, men subtotal pubertet senere i forløbet afløses af en spontan pubertet. Den spontane pubertet hos ubehandlede viser sig at medføre meget langsom stigning af fosfatase koncentrationen (måneder til år), mens choriongonadotropinbehandling kan fremkalde stigningen overmåde hurtigt (uger til få måneder).

Ved at følge fosfatasekoncentrationen under en choriongonadotropinserie kan man få oplysning om den spontane testishormonproduktion, om testes' og prostatas funktionelle „beredskab", om testes' maksimale evne til hormonproduktion, respektive prostatas evne til fosfataseproduktion og om testes' evne til — een gang stimulerede — at fortsætte hormonproduktionen. Endelig kan der af forløbet udledes visse slutninger om hypofysens og testes' indbyrdes forhold. Så godt som alle undersøgte hypandrine i pubertetsårene reagerer med testishor-

monproduktionen under 1. serie (1500 I. E. Physex Leo × ca. 30 over ca. 3 måneder), men kun hos de færreste opnås normal fosfataseproduktion.

Det vises, at årsagen til dette sidste ikke er, at den valgte dosis er for lille.

Efter behandlingens ophør vedvarer testishormonproduktionen (provokeret pubertet) hos nogle og ophører pany (pubertetsimitation) hos andre.

Det vises ved behandling med een serie choriongonadotropin af 19 tidligere ubehandlede hypandrine med primært manglende fosfataseproduktion (hvoraf 2 ikke reagerede), at alle 6 dystrofia adiposo-genitalis patienter reagerede med provokeret pubertet, mens 8 af de 11 patienter fra infantilismusgruppen (d. v. s. infantilismus, pubertas tarda, eunuchoidismus) kun opnåede en pubertetsimitation. Forskellen kan ikke forklares ved forskel mellem de to patientgrupper i alder, testisvolumen, behandlingsintensitet eller observationstid.

Forklaringerne på, at det overhovedet er muligt at opnå provokeret pubertet gennemgås. Det formodes, at hypofysen hos dystrofia adiposo-genitalis patienter producerer tilstrækkeligt gonadotropin til at vedligeholde en med udefra tilført hormon startet testisfunktion. De 4 af de 6 med denne lidelse viser en hypofysefunktion, der ikke kunne have været bedre hos normale drenge.

Med støtte i litteraturen drages den konklusion af fosfatasereaktionen ved dystrofiaadiposo-genitalis, at disse patienter næppe er patologisk hypandrine, og at deres hypofysefunktion er — i hvert fald potentielt — normal.

Da normale drenges fosfatasereaktion på choriongonadotropinbehandling ikke er undersøgt i dette arbejde, må spørgsmålet, om den ofte subnormale fosfatasereaktion er et tegn på dårligt fungerende testes, eller om den er fysiologisk netop i den alder lades åbent. Nogen større testesdefekt kan dog ikke være til stede hos dystrofia adiposo-genitalis patienterne, eftersom hormonproduktionen holder sig efter behandlingen.

Den provokerede, subnormale fosfataseproduktion afløses ofte efter måneders til års forløb af en spontan stigning til normale værdier, antagelig som udtryk for en spontant øget testishormonproduktion.

Behandling af patienter i infantilismusgruppen med gentagne

serier af choriongonadotropin vil oftest mindske latenstiden og bedre den midlertidige fosfataseproduktion; men kun hos 2 af 7, hos hvem reaktionen på 1. serie var en pubertetsimitation, fremkaldtes provokeret pubertet ved gentagen behandling. Hos en del patienter ses spontan stigning i fosfatasekoncentrationen lang tid efter at behandling er seponeret. Denne stigning findes at være udtryk for en intensivering af pubertetsprocesserne, der muligvis ville være indtruffet selv om den tidligere behandling ikke havde været institueret.

Der gives en oversigt over de kombinationer af pubertetsimitation, spontan og provokeret pubertet, der forekommer hos samtlige de med choriongonadotropin behandlede hypandrine (ialt 36). Det vises, at en imitation kun i ca ⅓ af tilfældene efterfølges af en provokeret eller spontan pubertet. Alderen synes her af afgørende betydning. Er patienten > 20 år, er chancen for, at imitationen afløses af pubertet, meget ringe.

En provokeret subtotal pubertet synes hyppigere blandt dystrofia adiposo-genitalis patienter end i infantilismusgruppen at blive afløst af en senere superponeret, spontan pubertet. Hos mange af patienterne er den provokerede pubertet, der opnås ved choriongonadotropinbehandling antagelig blot en foruddiskontering af den testishormonproduktion, der alligevel senere ville være sat ind spontant.

Kapitel XVIII. Relationen mellem kønsmodningstypen og det opnåede kønspræg.

Paa grund af sin inegale sammensætning er materialet mindre egnet til, at man kan foretage sammenligning mellem den opnåede kønsmodningsgrad og den foreliggende kønsmodningstype.

Det påvises dog, at den kønsmodning, der fremkaldes af en total (provokeret eller spontan) pubertet er større end ved imitationen, med hvilken det er vanskeligt trods intensiv behandling at opnå normalt testisvolumen og terminalbehåring svarende til alderen. Uden anvendelse af fosfatasereaktionen er det som nævnt vanskeligt at diagnosticere arten af testisreaktionen på behandlingen, men det findes, at muligheden er stor for, at der trods intensiv behandling kun opnås pubertetsimitation, når den behandlede er en patient fra infantilismusgruppen over 20 år med små testes.

Endelig findes det, at den spontane pubertet indtræder tidligere hos dystrofia adiposo-genitalis patienterne end i infantilismusgruppen.

Kapitel XIX. Choriongonadotropinbehandlingens indflydelse på fosfatasekoncentrationen og på den renale udskillelse af gonadotropin, androgene og østrogene stoffer.

6 patienter følges med urinhormonanalyser i tilslutning til en choriongonadotropinserie. Stigningen i androgenurien findes at være et lige så eller mere følsomt kritreium på testisstimulation end stigningen i fosfatasekoncentrationen. Påfaldende nok kan fosfataseproduktionen (d. v.s. testishormonproduktionen bedres varigt, samtidig med at forøgelsen i den renale udskillelse af gonadotropin, androgen eller østrogen er forbigående.

Kapitel XX. Om retningslinier for behandling af hypandrine med choriongonadotropin på grundlag af fosfataseproduktionens forløb.

Det vises ved hjælp af fosfatasereaktionen, at hypergonadotropinuri hverken udelukker pubertetsimitation eller provokeret pubertet. Forklaringen herpå er antagelig, at choriongonadotropinbehandlingen i de anvendte doser er et langt kraftigere incitament over for testes end selv en forhøjet hypofysegonadotropinproduktion. Omvendt udelukker normal gonadotropinuri ikke, at der kun opnås pubertetsimitation. Det formodes, at hypergonadotropinuri er et for følsomt kriterium for testes' tilstand til at være af afgørende prognostisk betydning.

Den kliniske bedring hos stærkt hypandrine under den første behandlingsserie er ret ensartet fra patient til patient og derfor ikke anvendelig som grundlag for en uddifferentiering af testes' reaktion på behandlingen.

Ved hjælp af fosfatasereaktionen er det derimod muligt at skelne mellem, om den første serie resulterer i en midlertidigt eller i en varigt øget testishormonproduktion, og derved — omend med et vist forbehold (se kap. XVII) — at skønne over effekten af senere choriongonadotropinserier.

Prognosen for det videre spontane forløb må ligeledes bedømmes med et vist forbehold ud fra fosfatasereaktionen, da såvel en pubertetsimitation som en provokeret subtotal pubertet senere kan afløses af en spontan pubertet (se kap. XVII).

Slutteligt diskuteres hovedretningslinierne for behandling med choriongonadotropin.

Ved dystrofia adiposo-genitalis vil det oftest være rationelt at undlade hormonbehandling, hvis eneste virkning som regel vil være at fremskynde en iøvrigt til normal tid indsættende pubertet. Er den spontane pubertet undtagelsesvis ikke begyndt omkring 15.—16. år, er behandling indiceret.

Ihvorvel behandling af infantilismusgruppen er væsentligt bedre indiceret også før det 16. år af hensyn til den ofte udebliverde, sene eller defekte spontane pubertet, må det dog fremhæves, at choriongonadotropin ofte kun vil fremkalde pubertetsimitation og i sådanne tilfælde ikke er mere virksomt end testosteron.

Foruden en chance for provokeret pubertet opnås med rettidig choriongonadotropinbehandling oftest en acceleration af længdevæksten og af epifysemodningen, hvorved opståelsen af eunuchoide proportioner forhindres eller modvirkes.

CASE RECORDS

Introduction.

R. H. m. P.:	Medical Outpatients' Department of the Rigshospital.
R. H. Dept. G.:	Department for Children's Diseases of the Rigshospital.
R. H. Dept. B.:	Medical Department B. of the Rigshospital.
R. H. Dept. C.:	Surgical Department C of the Rigshospital.
Private patient:	Patients not hospitalized or treated in Outpatients' Department.

The numbers under the heading of each case record refer to the pages, figures and tables respectively, on which the case is dealt with.

The state of the patient is described up to the date on which the first attempt at expression was made. The state on this day is termed: **Status.** All relative dates in the past history refer to this date.

A brief account is given of the physical state of the patients whose measures are stated in one of the tables, to which reference is made in such case.

Treatment with Phyol A. B. has not been stated for the following reason: None of the hypandrogenic patients examined here who have been treated with Phyol have shown changes in the phosphatase production which can be due to the Phyol treatment; the doses employed have been from 1 to 2 ml of Phyol 3 × daily. According to *Horstmann* (1949), who has examined several of the patients dealt with in this work, the preparation has not had any demonstrable effect on the body growth.

No. 1: Eunuchoidismus.
R.H. m.P. 744/40, born on 15th December 1924.
Table XV.

Has not had parotitis or orchitis. Applied in 1940 on account of increase in weight.

Physical exam. 1940. Moderately diffuse obesity. Vigorously developed mammae. Testes very small, located at a high level, the right one in the inguinal canal, the left can be descended. Penis of normal size, 5 cm. long. Vigorous growth of pubic hair.

Treatment. May — August 1940: 500 I. U. of Physex × 30 without certain effect. October — December 1944: 500 I. U. × 10 for 20 days, then 1500 I. U. × 20 for 60 days. This therapy produced frequent and long-lasting erections, which ceased one month after the discontinuance of the treatment. No effect on the position or size of the testes or on the growth of beard.

Status 13th February, 1945. Age 20.2.

A certain libido with erection. No pollutions or ejaculations even by masturbation. At rare intervals a haemorrhagic fluid is disharged per urethram. Began shaving 2 years ago. Shaves every fortnight. The voice still infantile.

Physical exam.: Not markedly eunuchoid. Deposits of fat as in the female. Mammae pointed and protrusive. Testes: the right one not in the scrotum, the left in the scrotum, nut-kernel-sized. Penis hypoplastic and short, 5-6 cm long. Prostate abnormally small and rather short, with upwards concave edge, about ½ cm high. Expression of rather ample watery secretion.

Vigorous development of pubic hair without sharply defined horizontal line. No linea alba hair. Lack of perineal, anal and other body hair, apart from the hirci which are scanty, barbae downy. See also p. 146.

No. 2: Impotentia coeundi.
R.H. m.P. 602/45, born on 23rd February, 1914.
Table XXIII.

Delicate until school-age and small. In childhood and later often affected with transient retentio testis inguinalis. Began shaving at the age of 18. Has 5 children. In July, 1944, severe trauma of the testes. Testes abnormally tender since then. At the beginning of November, 1944, commencing obesity, decreasing growth of beard, impotentia erigendi and impeded orgasm as compared to previously 2-3-4 ejaculations every night. Libido unchanged. Shaves now every fourth day, previously every second day.

Status 7th February, 1945. Age 30.11.

Physical exam.: Even deposits of fat. Hips rather slim. Voice deep. Genitalia

externa normal. Prostate normal. Sella turcica: nothing abnormal. Eye examination: nothing abnormal. Renal hormone excretion: 0(< 50) M. U. of gonadotropic, 8 I. U. of androgenic and > 20- < 50 M. U. of oestrogenic hormone per diem. See also p. 166.

No. 3: Eunuchoidismus.
R.H. m.P. 2217/43, born on 30th March 1924.
p. 109, Fig. 11, Table XVII.

Applied to the Out-Patients' Department in July 1943. His only complaint is lacking growth of beard. Libido normal. Never pollutions. Seldom erection. Never coitus.

Physical exam. July 1943.: Voice infantile. Genitalia externa normal. Pubes normal. No barbae. Sella turcica: nothing abnormal. Renal hormone excretion: 30 R. U. of gonadotropic, 13 C. U. of androgenic and < 20 M. U. of oestrogenic hormone per diem.

Treatment. Physex 1500 I. U. × 33 from 30th May 1944 to 13th November 1944.

Physical exam. May 1944. Normal and frequent erections. Masturbation about twice weekly. Voice still infantile. No barbae.

Physical exam. October 1944. Libido normal. Voice deeper. Still no barbae. Examination of semen: 2.5 ml. + amount spilt. Appearance natural. Consistency tenacious. Fertility moderately decreased.

Status 23rd February, 1945. Age 20.10.

The condition unchanged from October 1944. Coitus about twice weekly.

Physical exam.: Genitalia externa well developed, testes very large. Prostate very low and soft, the bone can be felt. See also p. 152.

No. 4: Dystrophia adiposo-genitalis (sanata).
R.H. m.P. 3758/44, born on 3rd August 1920.
Table XVII.

His maternal grandmother had diabetes, his mother myxoedema. Increasing fatness since his 11th year. Puberty normal, about the age of 14-15. Penis has, however, always been underdeveloped; coitus can be performed, though with difficulty.

Physical exam. (October 1944): Metabolism 97-101 per cent. Renal hormone excretion: < 50 M. U. of gonadotropic and 25 I. U. of androgenic hormone per diem.

Treatment. Physex 1500 I. U. × 25 from 4th October, 1944, to 10th February, 1945.

Status 28th February, 1945. Age 24.6.

Normal libido, erection and growth of beard.

Physical exam.: Some diffuse truncal obesity, slim limbs. Testes of normal size, though rather small. Length of penis 7 cm. Terminal hair normal. See also p. 152.

No. 5: Eunuchoidismus.
R.H. m.P. 2311/40, born on 24th May, 1913.
Table XVII.

Consulted the Out-Patients' Department in 1940 for eunuchoidism.

Physical exam. (1940). High pitched voice. Testes like canary birds' eggs. Penis 4-5 cm long, with pointed glans. Sella turcica 9 × 7 square mm, i. e. too small. The shape normal. X-ray photo of carpus: Open epiphyses.

Renal hormone excretion: < 30 R. U. of gonadotropic, 8 C. U. of androgenic and 20 M. U. of oestrogenic hormone per diem.

Treatment: Physex 500 I. U. × 179 from 1940 to 1943, and 1500 I. U. × 38 during 1943-1944 with good effect.

Status 3rd March, 1945. Age 31,10.

Normal libido and potentia coeundi. Shaves once weekly. Voice virile.

Physical exam.: Testes of normal size, though somewhat small. Pubes normal. Voice virile. See also p. 152.

No. 6: Impotentia coeundi.
R.H. m.P. 3993/44, born on 5th April 1899.
Table XXIII.

Since 12th October 1944 treated for sinus bradycardia with ephedrine and nitroglycerine with good effect. Many nervous complaints, matrimonial controversies. The last two weeks impotentia erigendi.

Status 12th March, 1945. Age 45.11.

Physical exam.: Genitalia externa, prostate and other sex characters normal. See also p. 166.

No. 7: Eunuchoidismus.
R.H. m.P. 1765/44, born on 19th May 1912.
p. 97, 99, 145, Fig. 6, 24, Table IX, XVII, XXVII.

Applied to the Department in April 1944 on account of lack of puberty, apart from slight growth of hair in the genital region. No libido. No growth of body in the last few years. Does not shave.

Physical exam. (1944). Gracile, of eunuchoid type. High pitched voice. Genitals small, scarcely corresponding to the age of 12 years. Right testis hazel nut-sized, left pigeon-egg-sized, both soft. A few pubic hairs, moderate axillary hair. Sella turcica: nothing abnormal.

Treatment. Physex 1500 I. U. × 33 in 1944. During treatment with Physex onset of libido, but no coitus. Commencing barbae, but shaves only once monthly. Four months after the last Physex injection libido again weak, coitus attempted, erection satisfactory, but pronounced ejaculatio præcox. Growth of beard again ceased.

Status 20th March, 1945. Age 32.10.

Physical exam.: The skin of the face wrinkled like that of an old woman, of castrate type. Testes: the right one bean-sized, the left: owing to varicocele it is difficult to judge of its size; it is extremely soft. Penis small, prostate soft, low, about 1 cm high, upwards concave upper edge. Exprimate thin watery. Renal hormone excretion: 50 M. U. of gonadotropic, 13 I. U. of androgenic and $<$ 20 M. U. of oestrogenic hormone per diem, see also p. 150.

Concerning the later development of the somatic sex characters, see p. 202.

No. 8: Infantilismus primarius.
p. 90, Fig. 3, 24, Table IX, XVII, XXVII, XXIX.
R.H. m.P. 4131/44, born on 21st May 1928.

The younger of two children. The family healthy. No diseases of childhood. The changing of teeth normal. Has always been small.

Physical exam. (1944). Body type infantile, not obese. His mental development corresponds to his age, not to his appearance. Genitalia like those of an 8-year-old boy. Testes like large beans.

Penis 4-5 cm., quite thin. No pubes or hirci. Sella turcica 11 × 8 square mm. Metabolism normal. Renal hormone excretion: $<$50 M. U. of gonadotropic, 2-3 I. U. of androgenic and $<$ 20 M. U. of oestrogenic hormone per diem.

Treatment. Physex 1500 I. U. × 23 during the winter of 1944-45, latest 23rd January, 1945, with good effect, the genitalia grew, the growth of pubic hair set in and the voice grew deeper.

Status 16th March, 1945. Age 16.10.

Potentia erigendi. No ejaculation.

Physical exam.: Has grown. The voice breaking. Testes somewhat small. Prostate small, firm, 1 cm. high. Rather ample pubic hair. No barbae. See also p. 150.

Concerning the later development of the somatic sex characters, see p. 203.

No. 9: Hypoplasia testis.
R.H. m.P. 1025/39, born on 21st May 1915.
p. 165, Table XVI, XXII.

Puberty set in at the age of 10 years. Since then pollutions every third

week. Applied to the Department in 1939, because they have been more seldom.

Physical exam. (1939). Adipositas particulary of the hips, nates and abdomen with striae distensae. Testes pigeon-egg-sized, penis small, ample hair, masculine. Sella turcica: nothing abnormal.

Status March, 1945. Age 29.10.

Libido present, but has not attemped coitus, as he feels psychically inhibited; thinks he is somatically sufficient.

Physical exam.: As in 1939. See also pages 150 and 164.

No. 10: Eunuchoidismus.

R.H. m.P. 2135/43, born on 8th July 1923.

p. 95, Table XVII.

Hospitalized for eunuchoidism in the Rigshospital, Department A, 1943.

Physical exam. April 1943: Sella turcica: size at the lower limit of the normal. Renal hormone excretion: < 30 R. U. of gonadotropic, 1 C. U. of androgenic and < 20 M. U. of oestrogenic hormone per diem.

Treatment: Testovirone 25 mg. × 14.

Status 12th April, 1945. Age 21.9.

Physical exam. July 1943 (R.H. m.P.): Of eunuchoid type. Voice juvenile. Testes pea-sized. Penis deficiently developed. Pubic hair scanty.

Treatment. Physex 1500 I. U. × 150 from 1943 to 1945, latest loth April 1945.

Potentia erigendi, no coitus or ejaculation. Does not shave.

Physical exam.: Voice unchanged. Testes hazel-nut-sized, of normal consistency, in the upper part of the scrotum. Penis enlarged, now distinctly hypertrophic. Prostate of normal size, firm consistency, pubes normal, scanty hirci, downy barbae. See also p. 152.

No. 11: Hypoplasia testis.

R.H. m.P. 2691/39, born on 1st October 1911.

p. 145, Table XV.

Applies on account of childless marriage. Desire for children for 6 years. Repeated semen examinations show aspermia. Since his 14th year a left-sided scrotal hernia, which has not caused inconvenience. Coitus normal. Denies venereal disease.

Status 23rd March, 1945. Age 33.5.

Physical exam. Habitus normal. A considerable left-sided varicocele. Both testes moderately atrophic, soft, pigeon-egg-sized. Penis normal. Growth of hair normal. Testis biopsy: Considerable degeneration in both testes. No spermiogonia or later stages, right: The Leydig cells in large, broad strands between the tubuli, left: A strong relative — possibly also absolute — hyperplasia of the Leydig cells, varying in degree in the different parts of the preparation. Prostate normal. Terminal hair normal. Renal hormone excretion: 38 R. U. of gonadotropic and 45 I. U. of androgenic hormone per diem. See also p. 146.

No. 12: Eunuchoidismus.

R.H. m.P. 3933/44, born on 19th November 1913.

p. 159, Fig. 24, Table IX, XVII, XXVII.

Has always weighed too much, the obesity mostly localized to the truncus. The condition in October 1944: No libido. Voice high, genitals undeveloped. Metabolism 88-101-86 per cent. Renal hormone excretion: 0(- 50 M. U. of gonadotropic, 10 I.U. of androgenic and 0(- 20) M. U. of oestrogenic hormone per diem.

Physical exam. Adipose castrate type with feminine localization. Some development of the mammae. Testes pigeon-egg-sized, soft. Penis 5 cm. long. Pubic hair scanty and sharply defined. Moderate hirci. No barbae.

Treatment. Physex 1500 I. U. × 57 from November 1944 to April 1945. This therapy produced libido, deepening of voice and growth of scrotum, which has become pendulous.

Physical exam. (March 1944): No decrease of fatness, mammae more pronounced, but voice deeper, genitals grown, testes enlarged, firmer, richer growth of pubic hair.

Status 3rd April, 1945. Age 31.5.

Commenced shaving 6-7 years ago, once weekly for the last 6 months, before then once monthly. Voice was breaking last winter. Some transient libido last summer. Potentia erigendi, total 20 pollutions, commenced last winter.

Physical. exam. Adipositas of the Fröhlich type. Mammae enlarged. Voice breaking. Right testis: Located at a high level in the scrotum, walnut-sized. Left testis: Normally located, hazel-nut-sized. Prostate small with upwards concave edge, consistency soft. Pubic hair sharply defined, normal hirci, barbae downy. See also p. 152.

Concerning the later development of the somatic sex characters, see p. 204.

No. 14: Impotentia coeundi.

R.H. m.P. 867/35, born on 18th April 1910.

Table XXIII.

Suffers from chronic hepatitis and from depressio mentis. Libido normal, but failing erection ability.

Status 20th April, 1945. Age 35.0.

Physical exam. Genitalia externa, prostate and other sex characteristics normal. See also p. 166.

No. 15: Impotentia coeundi.

R.H. m.P. 991/40, born on 22nd May 1892.

Table XXIII.

Libido weak, therefore coitus at months' intervals only. Potentia coeundi normal.

Status 21st April, 1945. Age 52.11.

Physical exam. Goose-egg-sized, left-sided varicocele. Testes, penis, prostate and other sex characteristics normal. See also p. 166.

No. 16: Eunuchoidismus.

R.H. m.P. 2089/42, born on 29th July 1924.

p. 73, Table XVII.

At the age of 16 operated upon for bilateral cryptorchidism. From his 16th to his 18th year vigorous growth, total 20 cm, but does not arrive at puberty.

Physical exam. (1942). Habitus eunuchoid, face and speech like that of a 14-year-old boy. Voice high, testes pigeon-egg-sized, soft. Penis 3 cm long. Beginning pubes (appeared a few months ago). No hirci, no barbae. Sella turcica: nothing abnormal. Eye examination: nothing abnormal. Renal hormone excretion: < 30 R. U. of gonadotropic, 3.5 C. U. of androgenic and < 20 M. U. of oestrogenic hormone per diem.

Treatment: Physex 1500 I. U. × 15 during August-September 1942, and 1500 I. U. × 26 during 1943.

Status 24th April, 1945. Age 20.8.

Libido and potentia erigendi are present, but not coitus or masturbation. Has shaved once weekly during the last 12 months. The voice broke during the Physex treatment and has remained deep since.

Physical exam.: Testes of normal consistency. Penis of normal size. Prostate somewhat smaller than normal, of normal firm consistency (height about 1½ cm). Pubes normal of masculine type, hirci absent, barbae downy. See also p. 152.

No. 17: Impotentia coeundi.

R.H. m.P. 1022/45, born on 3rd March 1911.

p. 109, Fig. 11, Table XXIII.

Suffers from myocarditis subacuta, extrasystolia of moderate degree. Failing libido. Previously treated with testosterone propionate in doses of 25 mg without effect.

Status 26th March, 1945. Age 34.0.

Physical exam. Genitalia externa, prostate and other sex characters normal. See also p. 166.

No. 18: Eunuchoidismus.
R.H. dept. C. 971/45, born on 14th July 1925.
p. 69, 73, 87, 99, 142, 159, Fig. 1a, 15, Table VII, VIII, IX, XVII.

At a health examination in 1943 lacking descensus testis sin. was found.

Treatment. Received 60 injections of Physex during 1943, producing weak potency and appearance of hirci, but growth ceased at the discontinuance of the injections. On 16th May 1944 mobilisatio testis sin., repositio testis dxt. in scroti sine orchidopexia. In May 1945 admitted to Department of the Rigshospital for inversio testis dxt., retentio testis sin., atrophia testis bilateralis permagna.

Status 13th March, 1945. Age 19.8.

Physical exam. Infantile habitus. Voice high pitched. Right testis: Not palpable with certainty, at most half-pea-sized, left at annulus, pea-sized. Prostate not felt with certainty. Nothing to express. Very scanty pubic hair, no hirci, no barbae. See also p. 150.

No. 19: Dystrophia adiposo-genitalis (sanata).
R.H. m.P. 2937/42, born on 13th April 1923.
Table XVII.

At the age of 10 he began getting obese, and striae distensae occurred. Otherwise no inconvenience.

Physical exam. (1942): Apart from the obesity, nothing abnormal. Genitalia externa normal. Sella turcica: Nothing abnormal. Eye examination: Nothing abnormal. Renal hormone excretion: $<$ 30 R. U. of gonadotropic. $<$ 4 C. U. of androgenic and $<$ 20 M. U. of oestrogenic hormone per diem.

Treatment: Physex 1500 I. U. $\times$ 18 during 1942 with no action on the adipositas. Fully potent, and engaged. Shaves every second or third day.

Status 26th March, 1945. Age 21.11.

Physical exam.: Moderate adipositas with striae coeruleae. Genitalia externa, prostate and other sex characters normal. See also p. 154.

No. 20. Dystrophia adiposo-genitalis (sanata).
R.H. m.P. 2262/39, born on 4th February 1924.
Table XVII.

Obese since his fifth year, but otherwise no inconvenience.

Physical exam. (1939): Moderate dystrophia adiposo-genitalis. No pubes, no hirci. Metabolism, eye examination, X-ray of sella turcica show normal conditions. Renal hormone excretion: $<$ 30 R. U. of gonadotropic, 2 C. U. of androgenic and 20 M. U. of oestrogenic hormone per diem.

Treatment: Physex (strength not stated) 3 times weekly, total 29 with excellent effect. Testes of normal size, penis long, pubic hair vigorous, beginning hirci.

Status 22nd March, 1945. Age 21.1.

Normal libido and coitus. Is married and expecting a child. Adipositas has disappeared.

Physical exam. Genitalia externa, prostate and other sex characters normal. See also p. 152.

No. 21: Dystrophia adiposo-genitalis (sanata).
R.H. m.P. 3136/40, born on 3rd June 1925.

Applied to the Out-Patients' Department owing to deficiently developed genitals.

Physical exam. (1940): State of nutrition considerably above the average. Testes pea-sized, both located in the scrotum. Sella turcica: Nothing abnormal.

Treatment: Physex, 250-500 I. U. $\times$ 85 from December, 1940, to September, 1942.

Status 23rd March, 1945. Age 19.9.

Physical exam.: Normally developed. Obesity subsided. Genitalia externa, prostate and other sex characters normal. See also p. 152.

No. 25: Hypertrophia prostatae.

R.H. m.P. 1677/45, born on 16th June, 1880.

p. 97, Fig 6.

Status 26th May, 1945. Age 64.11.

Disposition to nycturia and pollakisuria.

Physical exam.: Genitalia externa normal. Marked diffuse enlargement of prostate, particulary of the upper part. Blood urea 84 m%, repeated two months later: 33 m%.

No. 27: Impotentia coeundi.

R.H. m.P. 1833/45, born on 22nd March, 1905.

Table XXIII.

Complaints: Headache, abdominal pain, pronounced nervousness. Typical attacks of hemicrania during the last 15 years. In 1936 his wife was bilaterally oophorectomized. Since then he has felt an aversion to coitus, which fatigues him much. Now coitus every third month only, with preserved potentia erigendi, but ejaculatio præcox.

Status 2nd June, 1945. Age 40.3.

Physical exam.: Genitalia externa, prostate and other sex characteristics normal. See also p. 166.

No. 28: Eunuchoidismus.

R.H. m.P. 3876/43, born on 18th October, 1920.

Table XVII.

At the examination of army recruits in 1940 he was found to be mentally retarded. Complaints: Weak libido, seldom erection, never ejaculation.

Physical exam. (November 1943): Tall; high voice, broad hips, mammae somewhat enlarged. Testes both walnut-kernel-sized, penis small. Secondary growth of hair scanty.

Treatment. Physex 1500 I. U. unknown how many times during 1943, and 1500 I. U. × 46 from January, 1944, to July, 1944. Then normal libido and normal coitus every 14th day. No pollutions. Shaves every fortnight.

Physical exam. (1944): Testes: Right 2.8 × 4.5, left 4.5 × 2.3. Penis 6.4 cm long and 2.6 cm thick.

Status 5th June, 1945. Age 24.8.

Normal erection, but some ejaculatio tarda. Coitus every fortnight. Shaves every 10th day.

Physical exam.: Normal habitus. Voice normal. Testes pigeon-egg-sized. Penis normal. Prostate small, with upwards concave edge, soft, 1 cm. high. Pubic hair scanty and sharply defined, hirci scanty, barbae downy. See also p. 152.

No. 29: Female intersex with hyperplasia adrenalis.

R.H. m.P. 1855/42, born on 25th September, 1924.

p. 93, Fig. 4.

Parotitis at the age of 6. Dentition normal. As an infant of normal size. Vigorous growth from the age of 7. Until her 12th year taller than children of the same age. At 12 cessation of growth. Voice breaking at the age of 8 to 9 years. Has shawed since the age of 18 to 19, now 2 or 3 times weekly.

Physical exam. (July 1942): Testes not palpable. Considerable enlargement of clitoris, looks like a small penis, but curved, the under-side fastened to the vulva. Hypospadia on the underside of the corpus a little behind the glans. Labia majora empty, meagre. In the vulva a narrow introitus. Pubic hair of feminine type, but scanty growth of hair along the linea alba. Sella turcica: Normal shape. Size 7 × 10 square mm, at the lower limit of the normal. Eye examination: Nothing abnormal. Height: 151 cm., weight: 45.1

kg. X-ray of epiphyses: Development more advanced than corresponding to her age. Renal hormone excretion: 18th August, 1942: 10 R. U. of gonadotropic, 60 C. U. of androgenic and 33 M. U. of oestrogenic hormone. 9th April, 1943: < 5 R. U. of gonadotropic, 6 C. U. of androgenic and > 20 M. U. of oestrogenic hormone. (18th July, 1945: about 50 M. U. of gonadotropic, 350 I. U. of androgenic and > 50 M. U. of oestrogenic hormone).

Status 16th June, 1945. Age 20.9.

Physical exam.: Small, slender, with gracile structure of bones. The somatic condition unchanged from 1942. On account of the projecting uterus it is difficult to find out by rectal exploration whether palpable prostatic tissue is present or not. Laparotomia explorativa revealed feminine genitalia interna. The ovaries atretic. The suprarenal glands markedly hyperplastic.

Microscopy of ovarian tissue: Fibrous atrophic ovarian tissue, in parts with a few atretic follicular cysts, but otherwise without signs of follicular maturation. No testicular tissue.

No. 30: Impotentia coeundi.

R.H. m.P. 2082/45, born on 1st October, 1886.

p. 97, Fig. 6, Table XXIII.

During the last five years increasing obstipation and slow discharge of the urine, furthermore nycturia; also impaired libido and erection ability.

Status 21st June, 1945. Age 58.8.

Physical exam.: Prostate not enlarged, but a little prominent, of homogeneous, firm consistency. Genitalia externa and the other sex characteristics normal. See also p. 166.

No. 31: Impotentia coeundi.

R.H. m.P. 2136/45, born on 1st August, 1916.

Table XXIII.

The last 7 to 8 years ejaculatio præcox (before immisio). Coitus 2 or 3 times weekly. Slight prostatism in the form of stitch in the urethra, imperious nisus, stranguria and pollakisuria.

Status 26th June, 1945. Age 28.10.

Testes very large, prostate and other somatic sex characteristics normal. See also p. 166.

No. 32: Cryptorchismus antea.

R.H. m.P. 1886/44, born on 3rd March, 1923.

Table XVII.

Renal hormone excretion (1944): < 50 M. U. of gonadotropic, 20 I. U. of androgenic and about 50 M. U. of oestrogenic hormone. The right testis has descended during previous Physex treatment (dose unknown). November 1943 Department C of the Rigshospital: Operatio pro retentione testis sin.

Status 3rd July, 1945. Age 22.4.

Physical exam.: Normal habitus. Testes: Right of normal size, position and consistency, left at the top of the scrotum and small, the size of a green walnut. Penis of normal size. Prostate a little below normal size, soft, consistency somewhat inhomogeneous. Pubic hair normal. See also p. 152.

No. 33: Hypoplasia testis.

R.H. Dept. B. Case record No. 620/45, born on 27th August 1886.

p. 165, Table XVII, XXII.

Puberty at the age of 14. He thinks that the testes have decreased and become softer since a parotitis in 1938. He also thinks that they become firmer and larger after injections of testosterone propionate, which he has received every spring since then. The treatment also relieves him of fatigue and impaired libido, from which he suffers every spring. Shaving every second day.

Status 28th August, 1945. Age 59.0.

Physical exam.: Rather fat, not of castrate type. Testes small and very soft.

Penis: Nothing abnormal. Prostate very small, flat and soft. Terminal hair normal. See also pages 152 and 164.

No. 35: Dystrophia adiposo-genitalis.
R.H. m.P. 1830/42, born on 4th March 1929.
p. 90, 197, 198, 264, Fig. 3, 24, Table IX, XVI, XXIV, XXVII, XXIX.

Habitus typical of dystrophia adiposo-genitalis. Potentia erigendi is present, but no pollutions or ejaculations, pubic hair extremely scanty, voice not breaking, does not shave.

Status 19th September, 1945. Age 16.6.

Physical exam.: Adipose with typical deposits of fat. Voice high. Testes situated at a high level in a small scrotum. Right testis of soft consistency, left of normal consistency. Penis small with pointed glans. Prostate small, ½ cm. high, soft. Expressed secretion watery. Pubes and hirci scanty. No barbae. See also p. 148.

Concerning the later development of the somatic sex characters, see p. 205.

No 36: Infantilismus secundarius.
R.H. m. P. 2746/41, born on 9th April, 1924.
p. 87, 90, 141, 142, 159, 264, 265, Fig. 1 b, 3, 24, Table VIII, IX, XVII, XXVII.

Two nephews of the mother are small. The mother operated upon for extrauterine twin pregnancy during pregnancy.

Weight at birth 2.5 kg. The primary dentition occurred late. Dentes lactici remained during thew secondary dentition. Could not walk or speak until he was two years of age. Retarded at school, although he began school late (7½ years). Enuresis nocturna.

Treatment. Elityran which had to be given up owing to intolerance. Received perandren for two years, 10 mg. × 2 weekly, until January, 1941, with doubtful effect. Grew 3-4 cm.

Physical exam. (1941): Proportions like those of an elderly pyknic. Almost white hair, adipose truncus, short neck, slender limbs. Voice high and squeaking, mental development not corresponding to his age. Testes not palpable, penis small, slack, phimosis. No accessory growth of hair. Sella turcica: Normal. Eye examination: Temporal blanching of the papilla. Renal hormone excretion: < 30 R. U. of gonadotropic, < 5 C. U. of androgenic and < 20 M. U. of oestrogenic hormone per diem.

Treatment: From October, 1941, to June, 1942,
Physex 1000 I. U. × 70
from August, 1942, to January, 1943,
Physex 1500 I. U. × 40
from December, 1943, to October, 1944,
tabl. gland. thyreoid.
300 I. U. daily
from October, 1944, to April, 1945,
Physex 1500 I. U. × 30.

Metabolism, January 1945: 87-85 per cent.

Status 5th September, 1945. Age 21.5.

No libido, erection or ejaculation. No change of voice.

Physical exam.: Right testis at the top of the scrotum, pea-sized, soft. Left testis at the bottom of the scrotum, hazel-nut-sized, firm. Prostate small. Pubic hair scanty. Other accessory growth of hair absent. See also p. 150.

Concerning the later development of the somatic sex characters, see p. 206.

No. 40: Impotentia coeundi.
R.H. m.P. 4025/45, born on 3rd April 1910.
p. 109, Fig. 11, Table XXIII.

During the last three years fatigue. Last 6 months increasing impotency. Denies veneral disease.

Status 15th November, 1945. Age 35.7.

Physical exam.: Genitalia externa, prostate and other somatic sex characters normal. See also p. 166.

No. 41: Infantilismus primarius.
R.H. m.P. 2464/45, born on 2nd July, 1930.
p. 159, Fig. 24, Table IX, XVII, XXVII, XXIX.

His mother small and with late development. His weight at birth: 2,500 gm, length at birth: 52 cm. As a child deficient in weight, therefore admitted to the Copenhagen County Hospital in Gentofte in 1941.

Physical exam. (July 1945): His appearance like that of a 12 or 13-year-old boy, gracile, normal proportions, testes nutkernel-sized. Scanty pubic hair. Sella turcica: Normal.

Treatment: From 28th July to 6th October, 1945, Physex 1000 I. U. × 32. During this treatment rather vigorous growth of pubic hair, but no hirci, barbae or erection.

Status 18th November, 1945. Age 15.4.

Physical exam.: Voice infantile. Testes small. Prostate palpable with difficulty, is rather firm. Ample pubic hair, though over a small area. No hirci, no barbae. Eye examination: Normal. 24-hour output of urine < 1 litre. See also p. 152.

Concerning the later development of the somatic sex characters, see p. 208.

No. 42: Infantilismus secundarius.
R.H. m.P. 2235/43, born on 13th December, 1924.
p. 87, 90, 95, 99, 141, 264, 265, Fig. 1 b, 5, 24, Table VIII, IX, XVII, XXVII.

Adipositas set in rather suddenly at the age of 9 to 10 years. Cessation of growth about his 14th year. Lack of puberty. Now fatigue, great thirst, ample discharge of urine (2 or 3 times nocte).

Physical exam. (July 1943): Small, pale and obese. Genitalia externa like those of a 10-year-old boy, testes well over hazel-nut size. No accessory hair. Basal metabolic rate: 76-76 per cent. Eye examination: Nothing abnormal. X-ray of skull: Nothing abnormal. Admitted to the Neuro-Medical Department of the Rigshospital 7th August to 15th September, 1943. Encephalogram: Apart from a slightly enlarged leftsided temporal horn and a large subarachnoid accumulation of air over the left hemisphere, nothing abnormal. Diagnosis: Meningo-encephalitis hypothalami. Renal hormone excretion: < 5 **R. U.** of gonadotropic <0.5 C. U. of androgenic and < 20 M. U. of oestrogenic hormone per diem.

Treatment: Physex 500 I. U. × 97 from September,1943, to March, 1945, with some effect: A little enlargement of penis, voice a little deeper. Grown 7 cm. No effect on accessory hair or weight; libido, erection (once weekly) unchanged. No pollution or ejaculation.

Status 20th August, 1945. Age 20.8.

Physical exam.: Voice high. Obese, with atypical "Fröhlich distribution". Testes hazel-nut-sized, penis small, prostate very small with upwards convave border, the bone palpable, height $<$ ½ cm. Consistency soft. See also p. 150.

Concerning the later development of the somatic sex characters, see p. 210.

No. 43: Castrationis seq.
R.H. m.P. 4219/44, born on 9th April, 1875.
p. 88, Fig. 2.

Twenty-five years ago bilateral orchiectomy on account of tuberculosis. Since then no libido. Shaves daily.

Status 19th November, 1945. Age 70.7.

Physical exam.: Looks younger than his age. The skin but little wrinkled. The face not of castrate type. State of nutrition just above the average. Scrotum empty. Prostate considerably diminished, but palpable.

No. 45: Hypoplasia testis.
R.H. m.P. 2881/43, born on 6th March, 1922.

Table XVI, XXII.

Testes and penis have grown but little since beginning of puberty. Pubic hair, beard and voice completely developed; course of development normal. Sexual functions normal, coitus normal.

Physical exam. (1943): Genitals like those of a 14-year-old boy. Testes soft. Accessory growth of hair normal.

Status 26th October, 1945. Age 23.7.

As in 1943. See also pages 150 and 164.

No. 46: Dystrophia adiposo-genitalis.

R.H. m.P. 3199/38, born on 25th November, 1926.

Table XVII.

No previous diseases apart from morbilli and rubeolae. Normally developed, but always a little inhibited owing to hardness of hearing. Always rather obese.

Physical exam. (1938): Adipositas of "Fröhlich distribution". No accessory hair. Sella turcica: Nothing abnormal.

Treatment: Physex, 68 injections (strength ?) from January, 1939, to May, 1939.

Status 12th December, 1945. Age 19,1.

Libido and potentia erigendi present. Began shaving in 1940, once or twice weekly.

Physical exam.: Voice high. Adipositas with normal deposits. Genitalia externa and prostate normal. Pubes normal, barbae downy. See also p. 152.

No. 47: Hypoplasia testis.

R.H. m.P. 574/44, born on 8th June, 1896.

p. 140, 169, 170, Fig. 3, Table XVI, XXII.

At the age of 20 to 22 years pulmonary tuberculosis. No symptoms hereof since. Complains of stitch at the heart (Physical exam.: Nothing abnormal). The examination reveals gynaecomastia and small testes. No complaints of reduced potency. Shaves since the age of 17, 3 times weekly (suffers from sycosis barbae).

Status 19th December, 1945. Age 49.6.

Coitus once or twice monthly (normal).

Physical exam.: State of nutrition about the average. Normal deposits of subcutaneous fat, breasts somewhat enlarged with glandular tissue in the left side. Testes somewhat small and soft. Prostate normal, left lobe even prominent. Consistency normal. 2½ cm high. Accessory growth of hair normal. See also pages 150 and 164.

No. 49: Infantilismus primarius.

R.H. m.P. 4414/45, born on 10th March, 1929.

p. 86, 87, 90, 96, 142, 196, 263, 264, 265, 266, Fig 1 a, 24, Table VIII, IX, XVI,

Mother small. Weight at birth 1½-2 kg. Has always been small for his age. Grown 10 cm from his 14th to his 16th year. Got on well at school. His voice cracked at the age of 16½ years. Does not shave.

Status 3rd December, 1945. Age 16.9.

Infantile without any accessory growth of hair. Sella turcica: nothing abnormal. Basal metabolic rate: 122—106 per cent. See also p. 148.

Concerning the later development of the somatic sex characters, see p. 212.

No. 50: Eunuchodismus.

R.H. m.P. 457/38, born on 9th November, 1914.

Fig. 15.

Is referred to the Outpatients' Department for hypoplasia testis and infantilism. 1924 orchidopexia sin. at Bispebjerg Hospital. Growth of beard started at the age of 15, but since downy barbae only. Shaves once weekly or at longer intervals.

Physical exam. February, 1938. Facies more puerile than his true age.

Testes: Right located high in the inguinal canal, can be descended to the annulus, is bean-sized, slack; left located in the top of the scrotum, is small, but firm. Penis small, but not pointed, 4 cm long. Pubes and hirci scanty, barbae downy. Voice puerile. Basal metabolic rate: 100-101 per cent.

Treatment. From August, 1938, to July, 1940: 200 M. U. of Physex × 250 distributed over several series, moreover testosterone propionate, 10 mg. × 29.

During the treatment the patient can practice coitus with orgasm and ejaculation. Discontinuance of the treatment decreases this ability. Married in 1940.

March-December, 1943: 1500 I. U. of Physex × 36, January, 1944: 1500 I. U. × 2. The same transient effect. Can perform coitus once weekly, but with deficient erection and scanty ejaculation.

Physical exam. April, 1945. Facies of castrate type, habitus eunuchoid. Slight adipositas of feminine distribution. Voice somewhat deeper than castrate voice. Testes: Both of normal consistency, situated tn the middle of the scrotum; right bean-sized, left hazel-nut-sized. Penis 40 mm long, 25 mm thick. Prostate small and rather soft. Barbae downy.

Status 1st December, 1945. Age 31.1.

Now again aspermatism, brief erection during coitus, seldom orgasm. Libido weak. Shaves twice weekly (his occupation requires that he is always clean-shaven).

Physical exam.: Eunuchoid body growth, facies of castrate type, voice high. Total testis volume: 2.8 ml., both firm, situated high in a small scrotum. Penis 45 mm long, 18 mm thick. Prostate is hardly palpable. Dense growth of pubic hair, but covering too small an area. Scanty hirci, barbae downy Height: 181.2 (height when sitting 83.5); weight 80.7. Renal hormone excretion: 0(- < 50) M. U. of gonadotropic, about 10(< 20) M. U. of oestrogenic and 25 I. U. of androgenic hormone per diem.

No. 51: Infantilismus primarius.
R.H. m.P. 4626/45, born on 19th December, 1927.
Table XVI.

Father small. The patient has always been small.

Status 27th December, 1945. Age 18.0.

Libido absent, last 18 months potentia erigendi (once weekly) no ejaculation. Has not yet started shaving. The voice possibly in proces of breaking.

Physical exam.: Well-proportioned, normal state of nutrition. Testes in the upper part of the scrotum, plum-sized, of normal consistency. Penis of normal size, glans a little curved, but well-developed. Prostate firm, prominent, 1½ cm high. Profuse growth of pubic hair, of masculine pattern. No barbae. Sella turcica: 12×6 square mm, normal. See also p. 150.

No. 52: Dystrophia adiposo-genitalis.
R.H m.P. 2307/44, born on 2nd April, 1933.
Table XVII.

After 1943 the patient, who had previously been slender and lively, began to get increasingly obese, dull and to lose interests. Sleeps 10 out of 24 hours. Great appetite. Attends a class for mentally retarded children.

Physical exam. (June 1944): Typical dystrophia adiposo-genitalis. Presence of gynaecomastia. Genitals: left testis in the scrotum, nut-kernel-sized. Penis very small. Sella turcica normal. Eye examination: Astigmatic hypermetrope.

Treatment: Physex 1000 I. U. × 40 from June, 1944, to April, 1945, and 1500 I. U. × 10 from September to November, 1945.

Status 18th December, 1945. Age 12.8.

No libido or potentia erigendi. No shaving. The voice in process of breaking.

Physical exam. Adipositas of the Fröhlich type, mammae enlarged with a little glandular tissue. Both testes in the scrotum, walnut-sized, of normal consistency. Penis small, glans of normal dimensions. Prostate firm, 2 cm high. Decrease of pubic hair. Hirci scanty. No barbae. See also p. 152.

No. 53: Hypoplasia testis.
R.H. m.P. 4643/45, born on 30th March 1921.
p. 164, 165, Table XVI, XXII.

Mumps at the age of 4, without orchitis. Otitis media at 15. Scarlatina at the age of 16 years. Onset of puberty about his 15th year; started shaving then, now 3 times weekly. Testes are said always to have been small, always in the scrotum. Libido just below the average. Coitus once weekly at the utmost. Often ejaculatio præcox. It has not been possible for the physician to demonstrate spermatoza by microscopy.

Status 28th December, 1945. Age 24.9.

Physical exam.: Not of castrate type, though somewhat long-limbed. Testes situated in the middle of the scrotum, size like that of a little bean, firm. Penis normal. Prostate normal-sized, rather firm. Profuse accessory growth of hair, barbae coarse. Voice normal. See also pages 150 and 164.

No. 54: Infantilismus primarius.
R.H. m.P. 4600/45, born on 16th December, 1929.
p. 196, 197, 264, 265, 266, Fig. 24, Table IX, XVI, XXIV, XXVII.

Mother small. Father and one of the two elder twin sisters of normal stature, the other small. The patient has always been small. Manages well at school and at his present work. Transitory glycosuria at the age of 7. Parotitis at the age of 12.

Physical exam. (1945): Small, well-proportioned, bright. Sella turcica 9 × 6 square mm, a little less than corresponding to his age.

Status 19th December, 1945. Age 16.0.

No subjective symptoms of puberty.

Physical exam.: Well-proportioned, but small. Voice high. Testes hazel-nut- to walnut-sized, normal consistency. Prostate of soft consistency, 1 cm high. Pubes: A few downs. No hirci or barbae. See also p. 148.

Concerning the later development of the somatic sex characters, see p. 214.

No. 55: Infantilismus secundarius.
R.H. m.P. 3615/45, born on 8th May, 1929.
p. 142, 160, 264, 265, Fig. 6, 24, Table IX, XVII, XXVII, XXIX.

An only child. Diabetes ascertained at the age of 4 years. Hospitalized several times. Parotitis at the age of 6. Was treated with regular insulin 0.8 ml + 0.8 ml retard., dicta pleta without sugar. Manages well at school. upper fifth form. Has always been smaller than other at the same age, this was most striking at the age of 14-15 years.

Treatment: Physex 1500 I. U. × 12 from October to 24th November, 1945.

Status 14th January, 1946. Age 16.8.

The voice has just commenced breaking.

Physical exam. Slight truncal obesity without "Fröhlich distribution". Testes plum-sized. Considerable phimosis. Pubic hair most scanty. No hirci, no barbae. Sella turcica 9 × 7 square mm, somewhat less than corresponding to his age. See also p. 150.

No. 56: Normal (thrombangiitis obliterans).
R.H. m.P. 4649/46, born on 1st October, 1895.
p. 97.

Status 3rd January, 1946. Age 50.3.

Physical exam.: Genitalia externa, prostate and other sex characters normal.

N. B. Is entered both in the series of normal individuals, table XI, p. 122 (concentration of phosphatase in first expressed secretion 9.1 K. P. U.) and under the patients that have undergone treatment with oestrogens in Figure 6, p. 98.

No. 58: Impotentia coeundi.
R.H. m.P. 2767/43, born on 8th March, 1912.
p. 102, Fig. 8.

Uncomplicated gonorrhea in 1936. Has always had deficient and rapidly ceasing erection. Married in 1927. Coitus fairly normal during the first three years of marriage, later gradual aggravation. Libido now weak, but he can practise coitus a few times monthly. Has one child. No matrimonial difficulties.

Treatment. A total of 400 to 450 androstin tablets and 20 injections of testosterone (strength?) without effect. Treatment ceased in the autumn of 1945.

Status 6th February, 1946. Age 33.11.

Physical exam.: Genitalia externa, prostate and other sex characters of normal development.

No. 59: Dystrophia adiposo-genitalis (in sanatione).
R.H. m.P. 2172/44, born on 3rd August, 1931.
Fig. 24, Table XVII, XXVII.

In 1941 his mother observed that his genitals were too small, only one testis is said to have been in the scrotum. Always had a predisposition to fatness; is slow to everything. In May 1944 was found typical dystrophia adiposo-genitalis. A suspicion of gynaecomastia. Genitalia externa small. Right testis in the scrotum, left felt in the inguinal canal. Pubic hair scanty.

Treatment. Physex 1000 I. U. × 30 from May to September, 1944.

Status 6th February, 1946. Age 14.6.

Does not shave. Scanty erections, no pollutions.

Physical exam.: Somewhat obese with acrocyanosis of the femora. Very profuse growth of pubic hair, scanty hirci, downy upper lip. Sella turcica: nothing abnormal. Eye examination: nothing abnormal. See also p. 152.

Concerning the later development of the somatic sex characters, see p. 218.

No. 61: Infantilismus secundarius.
R.H. m.P. 1047/44, born on 6th September, 1926.
Table XVII.

Both parents are small (164 and 150 cm). Complaint: Stunted growth. Diabetes mellitus from his 5th year. Until the age of 14-15 years strict diet, since then a full diet, without sugar. As a child tall for his age, but has not grown since his 14th year.

Physical exam. (1944): Appearance and voice infantile. Presence of pubes. Hirci and barbae absent. Sella turcica: 7 × 11 square mm, nothing abnormal. Eye examination: Nothing abnormal. X-ray of carpus shows development corresponding to the 14th-15th year. Renal hormone excretion: < 30 R. U. of gonadotropic, < 20 M. U. of oestrogenic and 2.5 C. U. of androgenic hormone per diem.

Treatment. Physex 1500 I. U. × 15 from October to November, 1945.

Status 12th March, 1946. Age 19.6.

Potentia erigendi is present, no pollutions. Shaves once weekly, started six months ago.

Physical exam.: Equal distribution of adipositas. Voice breaking. Both testes in the top of the scrotum, of normal size and consistency. Penis normal. Pubic hair normal, scanty hirci, downy barbae. See also p. 152.

No. 63: Dystrophia adiposo-genitalis.
R.H. m.P. 452/46, born on 23rd May, 1933.
p. 198, Fig. 24, Table XVI, XXIV, XXVII, XXIX.

Applied to the Department for dystrophia adiposo-genitalis. At the age of 11, poliomyelitis without paralyses. Hereafter the patient who has always been plump suddenly became very stout. Got on tolerably at school, but was a little dull. Suffers from fatigue.

Status 30th January, 1946. Age 12.8.

Physical exam.: Marked adipositas, particularly localized to neck and trunck. Slight reddening of the skin of the face. Abdomen adipose without striae. The skin of the extremities slightly bluish red. Genitals like those of a 5-year The skin of the extremities slightly bluish red. Genitals like those of a 5-year-

old boy, testes in the scrotum. Basal metabolic rate: 85 per cent.-83 per cent. Concentration of erythrocytes: 5.46 mill./cubic mm. See also p. 148.

Concerning the later develonment of the somatic sex characters, see p. 218.

No. 64: Eunuchoidismus.
R.H. m.P. 449/46, born on 28th March 1916.
p. 163, Table XVI.

Mumps at the age of 7, without swelling of the testes. Clever at school. Always a little smaller and more slender than children of his age. In 1944 in German concentration camp for eight months. Had oedemas and wounds on the legs. Recovered rapidly after returning home. Complaints: Deficient development of genitals, falsetto. Libido is present, but coitus not attempted. Erection 3 times weekly. No ejaculation or pollution.

Status 26th January, 1946. Age 29.10.

Physical exam.: Thin long-limbed castrate-type with rather large hands and feet. The face gracile with thin skin. Voice high. No glandular tissue in the breasts. Both testes of normal size in pendulous scrotum; penis long, but thin and pointed. Prostate just below average size, rather flat, firm. Slightly pronounced pubes of feminine pattern. Some growth of anal hair. No hirci, no barbae. Sella turcica: 13 × 10 square mm, nothing abnormal. See also p. 150.

No. 65: Sexually mature dwarf.
R.H. m.P. 835/46, born on 19th February, 1928.
Table XVI.

From birth to the age of about 8 years suffered from cramps and absences. From 8th to 16th year only absences. Always of stunted growth. Growth ceased after his 14th year. Onset of puberty in his 11th year.

Status 19th February, 1946. Age 18.0.

Physical exam.: Dwarf. The extremities comparatively short. Genitalia externa, prostate and other sex characters fully developed. Sella turcica 8 × 7 square mm, at the lower limit of the normal. See also p. 150.

No. 66: Dystrophia adiposo-genitalis.
R.H. m.P. 1037/46, born on 23rd March, 1930.
p. 87, 90, 268, Fig 1 b, 24, Table VIII, XVI, XXIV, XXVII.

Previously normal. During the last twelve months more obese without any change of diet. Complains also of too small genitals.

Status 2nd March, 1946. Age 16.0.

Physical exam.: Obesity of "Fröhlich distribution". No striae. Moderate congestion to the face. Tender glandular tissue in the mammae. Diameter of the testes about 1 cm, consistency firm. Penis small, but not pointed. Very slight growth of pubic hair. Otherwise no growth of terminal hair. Blood pressure 160/90, 150/90. Eye examination: Nothing abnormal. Sella turcica: 10×8 square mm. Basal metabolic rate: 92-91 per cent. See also p. 148.

Concerning the later development of the somatic sex characters, see p. 219.

No. 67: Dystrophia adiposo-genitalis (sanata).
R.H. m.P. 1131/37, born on 14th May, 1921.
Table XVII.

Father obese. The patient suffered from diphteria in 1930, since then obesity and frontal headaches. Clever at school.

Physical exam. (1937): Severe, diffuse adipositas, particularly localized to hips and mammae, abdomen and face. Scanty growth of pubic hair. No hirci, slight growth of beard.

Treatment. Physex 100 I. U.×118 and diet for reducing weight.

Status 5th March, 1946. Age 24.10.

Apparent increase of libido. Ejaculation two or three times weekly, but urge for masturbation daily. Shaves once daily. Fat on abdomen and mammae (no

palpable glandular tissue); presence of pale striae. Genitalia externa and prostate normal. Profuse growth of terminal hair. Basal metabolic rate: 88-87 per cent. See also p. 152.

No. 68: Dystrophia adiposo-genitalis.
R.H. m.P. 3416/45, born on 26th March, 1933.
p. 142, 197, 198, 266, Fig. 24, Table IX, XVI, XXIV, XXVII, XXIX.

Bilateral pneumonia at the age of 8. Has always been obese, especially during the last 12 months, during which the weight has increased from 52 to 59.5 kg. Less disposition to perspiration than normally, is susceptible to cold. Manages well at school. Physically lazy during the last few months. Basal metabolic rate, September, 1945: 71-79, October, 1945: 89-72 per cent.

Status 3rd January, 1946. Age 12.9.

Physical exam.: Typical "Fröhlich localization" of adipositas. Genitals small, puerile. Testes well over hazel-nut-size, no hirci, no barbae. See also p. 148.

Concerning the later development of the somatic sex characters, see p. 220.

No. 69: Eunuchoidismus.
R.H. m.P. 4700/45, born on 30th May, 1921.
p. 86, 87, 99, 142, 159, 160, Fig. 1 a, Table VIII, IX, XVII.

At the age of 8 to 10 years operated upon for hernia inguinalis utr. Up to that time his genitals are said to have been naturally developed, corresponding to his age. During his 12th to 13th years one testis passed up into the abdomen. On account of lack of puberty the patient received injections 3 or 4 years ago, and "a substance was implanted" in the left nates with rather good, but transient, effect: Growth of penis, increased growth of axillary and pubic hair. No growth of beard. At rare intervals erections.

Status 31st December, 1945. Age 24.7.

Physical exam.: Thin, lanky, long extremities, eunuchoid. Scrotum small, left testis 1×0.5 cm, a little soft. In the right half of the scrotum is felt a pea-sized body (testis?). Penis 6 cm long, as thick as a little finger. Prostate not palpable; scanty pubes and hirci. No anal hair, no growth of beard. Sella turcica 12×8 square mm. See also p. 150.

No 70: Dystrophia adiposo-genitalis.
R.H. m.P. 1099/46, born on 24th July, 1932.
p. 142, 197, 198, 266, Fig. 24, Table IX, XVI, XXIV, XXVII, XXIX.

At the age of 2½ years tub. pulm., treated with gold salts; no inconvenience since. In 1940 mumps without testicular swelling. In 1941 scarlatina and diphtheria. From the age of 6 to 7 increasing obesity, particulary localized to the nates, the abdomen and the neck; the genitals have always been retarded in development. Rather indolent, but clever at school.

Status 6th March, 1946. Age 13.8.

Physical exam.: Obesity of "Fröhlich distribution". No striae. Some congestion to the face. Mammae very adipose, but no glandular tissue. Testes very small, like those of a 3-year-old boy. No terminal hair. Sella turcica: 10×9 square mm, nothing abnormal. Eye examination: Nothing abnormal. Concentration of erythrocytes: 4.31 mill/cubic mm. See also p. 148.

Concerning the later development of the somatic sex characters, see p. 221.

No. 72: Sexually mature dwarf.
R.H. m.P. 2071/44, born on 4th March, 1928.
Table XVI.

Father's family of small stature. Three sisters of normal stature. The patient has been suffering from rickets during infancy. Always of stunted growth. Onset of puberty about the age of 14 to 15.

Growth of beard scanty, shaves once monthly.

Physical exam. (1944): Genitals well-developed. Terminal hair normal.

Treatment. Tabl. gland. thyreoid. No. 2, 1×2 for two months in 1944.

Status 22nd March, 1946. Age 18.0.

Shaves twice weekly. Libido normal. Pollution or ejaculation once or twice weekly.

Physical exam.: Testes large, profuse pubic hair, normal hirci. Sella turcica. 11 × 8 square mm. nothing abnormal. See also p. 150.

No. 74: Infantilismus secundarius.
R.H. m.P. 2720/45, born on 23rd November, 1928.
Fig. 24, Table IX, XVI, XXIV, XXVII.

Recurrent bronchitis since the age of 1 year. Asthma bronchiale for the last 6 or 7 year.

Physical exam. (1945): Small, well-proportioned. Genitalia externa infantile.

Status 27th March, 1946. Age 17.4.

Physical exam.: Voice infantile. Testes rather small, but within the limits of the normal. Beginning pubes, no hirci, no barbae. Sella turcica: 12 × 8 square mm, nothing abnormal. See also p. 148.

Concerning the later development of the somatic sex characters, see p. 222.

No. 76: Hypoplasia testis.
R.H. m.P. 1230/42, born on 28th May, 1907.
p. 164, Table XVI, XXII.

Mumps at the age of 5. No orchitis. From early youth cardiac neurosis, particularly from his 12th to 14th year. Later during his work as a gardener he had to be exempted from hard work. In 1936 colitis. As a child and now and then as adult retentio testis. At 17 he was told that he was infertile. Puberty as late as at the age of 20 years. Gonorrhea many years ago, rapid recovery, no complications.

Status 4th April, 1946. Age 38.11.

Libido always slightly impaired. Coitus every 14th day. Has two children, 10 and 13 years of age.

Physical exam.: Somatically normal habitus, voice virile. Testes too small, the left one situated in the middle of the scrotum. Prostate very soft, nodular. Rich growth of terminal hair. See also pages 148 and 164.

No. 78: Hypoplasia testis.
R.H. m.P. 1681/46, born on 10th July, 1905.
Table XVI, XXII.

Left kidney excised in 1944, as far as is known because of renal calculi. Symptoms of gastric ulcer for the last month. Parotitis with orchitis at the age of 16. No children in spite of desire for children for 12 years. Libido impaired during he last three years owing to frigidity in wife. Previously coitus three times weekly. Shaves twice weekly.

Status 11th April, 1946. Age 40.9.

Physical exam.: Testes too small, prostate rather firm, a little nodular, normal-sized. Profuse terminal hair. See also pages 150 and 164.

No. 79: Infantilismus secundarius.
R.H. m.P. 1365/46, born on 4th October, 1926.
p. 87, 90, 95, 142, 181, 182, 183, 196, 197, 181, 264, 265, Fig. 1 b, 5, 24, Table VIII, IX, XVI, XXIV, XXVII.

No exanthematous diseases in the mother during pregnancy. Father and eldest brother died of tuberculosis. The patient is controlled once yearly. Is the youngest of 8 children, the others normal. Is a twin, the other twin is normal. Pyelitis at the age of six weeks, then whooping cough. Was confined to bed for twelve months, but recovered quickly and reached the stature of his twin brother at the age of 2½ years. Dentition at normal time. Since the beginning of 1932 slow growth and failing development. Was bad at school. Intelligence quotient: 79. Ultimo 1932 concussion of the brain. Enuresis nocturna. Stools normal. Fatty stools never observed.

Status 22nd March, 1946. Age 19.5.

Physical exam.: Habitus as in a 10-year-old boy. Slight diffuse adipositas. Face wrinkled like that of an old man, with yellowish tinge and with slight mimics. Psyche infantile, but stagnant. Voice infantile. No eruption of wisdom teeth. Genitals like those of a 2-year-old boy. Scrotum small, somewhat pigmented. Testes very small, size half of a pea, firm. Prostate scarcely palpable. No terminal hair. Output of urine 1 litre. X-ray of the skull and the sella turcica: Nothing abnormal. Eye examination: Nothing abnormal. Wassermann reaction negative. No albumen or pus in the urine. Metabolism: 97—107 per cent. See also p. 148 .

Concerning the later development of the somatic sex characters, see p. 224.

No. 80: Infantilismus primarius.

R.H. m.P. 1654/46, born on 15th August, 1931.

Fig. 22, Table XVI.

Mother small, father and a 11-year-old brother of average stature. The patient was small at birth (weight at birth: 2 kg.), always smaller than others of the same age. Did well at school. In childhood, cryptorchidism. Spontaneous descent of testes.

Status 9th April, 1946. Age 14.8.

Physical exam.: Both testes at the bottom of the scrotum. Incipient, but weak growth of pubic hair. No terminal hair. Sella turcica: 11×8 square mm, nothing abnormal. See also p. 148.

No. 94: Infantilismus primarius.

R.H. m.P. 1935/46, born on 22nd July, 1931.

Table XV.

The father is said to have been very small until the age of 16—18 years; then he started growing. Both parents and the four younger brothers and sisters of normal height. The patient had uncomplicated scarlatina at the age of 12. Until his 10th or 11th year his height was the same as that of others of the same age; since that time he has grown but little. Got on well in school. Is now an apprentice.

Status 30th April, 1946. Age 14.9.

Physical exam.: Small, well-proportioned, quite infantile. Testes normal, corresponding to his age. Prostate infantile. No terminal hair. See also p. 148.

No. 97: Infantilismus primarius.

R.H. m.P. 1485/46, born on 6th March, 1932.

p. 142, 197, 198, 266, Fig. 21, Table IX, XVI, XXIV, XXVII, XXIX.

Previously thin and lanky, but increased in weight during the last 18 months. Lost 7 kg. during the last two weeks after a fasting cure. During a recent stay at hospital (scarlatina) it was observed that the testes were small.

Status 30th March, 1946. Age 14.0

Physical exam.: Slightly adipose, but without unquestionable"Fröhlich distribution". Infantile habitus. Testes small, pubes not yet appeared. Basal metabolic rate: 100—104 per cent. Sella turcica: 9×8 square mm, nothing abnormal. See also p. 148.

Concerning the later development of the somatic sex characters, see p. 226.

No. 98: Dystrophia adiposo-genitalis.

R.H. m.P. 2317/46, born on 16th February, 1932.

p. 183, Table XVI, XXIV.

At the age of twelve months pneumonia. At the age of 4—5 years trauma of the fork, on which occasion something is said to have been crushed. In June 1945 commotio cerebri with loss of consciousness. Since 1942 he has grown more obese than his friends. Otherwise in well-being. Spontaneous descent of the testes in 1946. No headaches. Normal output of urine. Eye examination: Nothing abnormal. Basal metabolic rate: 110—82 per cent.

Status 15th May, 1946. Age 14.3.

Physical exam.: Bright and lively, infantile. Diffuse adipositas, chiefly of "Fröhlich distribution". Hypertrophia of the mammae with oedematous areolae and a considerable amount of glandular tissue. No striae coeruleae. The cheeks red, but no facies lunata. Testes small, prostate small, but firm. Scanty pubes and hirci, no barbae. Sella turcica: Nothing abnormal. See also p. 148.

No. 100: Dystrophia adiposo-genitalis (sanata).

R.H. m.P. 1789/39, born on 17th May, 1925.

Table XVII.

Since his 12th year increasing adipositas. No effect of treatment with thyroidea. Suffers from enuresis nocturna. Output of urine normal.

Physical exam.: Typical dystrophia adiposo-genitalis of "Fröhlich distribution". Testes of normal size corresponding to his age. Penis 3½ cm long. Large prepuce. Beginning pubic hair.

Treatment. Physex (how much?).

Status 28th May, 1946. Age 21.0.

Libido weak. Ejaculation once monthly. Shaves 3 times weekly.

Physical exam.: Diffuse adipositas, chiefly of "Fröhlich distribution". Testes normal. Prostate rather large, but soft. Very profuse growth of terminal hair. See also p. 152.

No. 101: Hypometabolismus (Normal variant?).

R.H. m.P. 1625/46, born on 2nd March, 1923.

p. 95, Fig. 5.

Has always been susceptible to cold, especially the fingers; most in winter, where he does not feel warm until late in the morning. Bowels sluggish, for the last two years, open only a few times weekly, even after laxatives. Since the autumn of 1945 taken two daily meals only. Has not eaten his fill. Has preferably eaten meat. Lost 8 kg during the last 6 months. At the end of March, 1946, a slight "influenza" (not confined to bed). Has not been tired. At the beginning of April swelling of ankles, abdomen and face, particularly in the evening, and increase of 2—3 kg in weight.

Physical exam. (8th April 1946): Not myxoedematous. Lean, but muscles in good form. Pulse rate 48. Diffuse oedema of the lower legs — increasing in the distal direction. Slight universal micro-adenitis. Wassermann reaction negative. Weight: 76 kg. Blood pressure? Serum protein total 5.80—6.0, alb. 5.46—5.40, glob. 0.61; determined at another laboratory 7.0, 5.3 and 1.7, respectively. Serum cholesterol 210 mg per cent. Specific gravity of urine: 1018. No albuminuria, no haematuria. Electrocardiogram: Bradycardia. The P-deflections not visible with certainty (muscular unrest). X-ray of the thorax: Nothing abnormal. Basal metabolic rate: 79—72 per cent. Rp. an unrestricted, ample diet.

15th April: The oedemas subsiding. Morning temperature for a week between 35.8° and 36.3° c. Evening temperature between 36.2° and 36.9°. Pulse rate correspondingly 39 and 46, and 42 and 45.

Status 3rd June, 1946. Age 23.3.

Physical exam.: As on the 8th April, but now no oedemas. Genitalia externa, prostate and other somatic sex characters normal. Fully virile terminal hair. Metabolism 76 per cent. Pulse rate 40. Renal hormone excretion: 6 C.U. (photometrically) and 5. C.U. (biometrically) of androgen per diem, respectively.

9th August: Weight 74 kg. Metabolism 74. Pulse 40.

31st August: Weight 75,5 kg.

No. 103: Infantilismus primarius.

R.H. m. P. 4236/45, born on 19th May, 1930.

Table XV.

Both parents small, but not dwarfs. The patient applied to the Outpatients' Department on account of being too small.

Physical. exam. (1945): Quite infantile. Sella turcica small, 8 × 7 square mm.

Treatment. Physex 1500 I.U. × 29 from 29th November, 1945, to 7th March, 1946.

Status 22nd May, 1946. Age 16.0.

Physical exam.: Habitus and genitalia infantile. Testes very small. Prostate not palpable. Pubic hair very scanty. No hirci, no barbae. See also p. 146.

No. 105: Gynaecomastia.

R.H. m. P. 2680/46, born on 31st December, 1925.

p. 169, 170.

Simultaneously with the onset of puberty, about the age of 15 years. growth of mammae was noted.

Status 11th June, 1946. Age 20.6.

Libido normal. Ejaculation once weekly. No coitus. Shaving once daily.

Physical exam. Not eunuchoid. Strong rubor faciei. Glandular tissue is felt in the mammae, nothing to express. Biopsy shows fatty tissue and connective tissue. Testes normal, prostate large, firm. Terminal hair normal. Basal metabolic rate: 89—87 per cent.

No. 106: Hypoplasia testis.

R.H. m.P. 3051/46, born on 21st November, 1896.

p. 141, 165, Table XIV, XVI, XXII.

Recurrent gastric disturbances during the last six years. Cardialgia, vomiting. No parotitis. Uncomplicated gonorrhea 25 years ago. Has always had small testes. Puberty rather early. He does not remember when body growth ceased. Has two children, 13 and 9 years old. Decrease of potency the last 4—5 years, but normal libido.

Status 6th July, 1946. Age 49.8.

Physical exam.: Both testes very soft. Left-sided considerable varicocele. Prostate rather small, but firm. Very profuse growth of terminal hair ("Monkey's hair"). See also pages 148 and 164.

No. 107: Impotentia coeundi.

R.H. m.P. 3085/46, born on 10th September, 1900.

p. 103, 145, Fig. 8, Table XXIII.

No venerea. Always rather weak libido. Lack of erection ability last six months, libido unchanged. Now and then ejaculation.

Status 9th July, 1946. Age 45.10.

Physical exam.: Genitalia externa and terminal hair normal. The size of the prostate at the upper limit of the normal, consistency firm, homogeneous. Some deposits of fat in the mammae, glandular tissue not palpable. See also p. 166.

No. 108: Infantilismus secundarius.

R.H. m.P. 339/46, born on 10th February, 1931.

p. 145, Fig. 22, Table XVI.

Congenital malformation of the heart (presumably pulmonary stenosis). No cyanosis. Has always been smaller and weaker than others of the same age.

Status 15th July, 1946. Age 15.5.

Physical exam.: Testes large. Beginning pubes over an area of a few mm in height. No hirci, no barbae. See also p. 148.

No. 109: Impotentia coeundi.

R.H. m.P. 3223/46, born on 22nd February, 1903.

p. 108, Fig. 9, Table XXIII.

During the last three or four months pruritus ani. Last two years impotentia erigendi. Libido unchanged. Coitus once weekly.

Status 19th July, 1946. Age 43.5.

Physical exam.: Genitalia externa, prostate and other somatic sex characters normal. See also p. 166.

No. 110: Impotentia coeundi.

R.H. m.P. 2665/46, born on 5th July 1912.

p. 146, Table XXIII.

Parotitis in the age of 15, without orchitis. 13 months in concentration camp. Since returning home in May, 1945, presence of libido, but failing erection ability, the erection being too brief. No ejaculation the last 1½—2 years, before then coitus two or three times weekly.

Status 7th June, 1946. Age 33.11.

Physical exam.: Genitalia externa, prostate and other somatic sex characters normal. See also p. 166.

No. 111: Impotentia coeundi.

R.H. m.P. 3160/46, born on 24th November, 1906.

Table XXIII.

Gonorrhea at the age of 20. No inconvenience since. Coitus once or twice weekly. Previously ejaculation two or three times during each coitus, now only once. Now also ejaculatio præcox.

Status 15th July, 1946. Age 39.8.

Physical exam.: Genitalia externa, prostate and other somatic sex characters normal. See also p. 166.

No. 112: Hypoplasia testis.

R.H. m.P. 2017/44, born on 23rd February 1914.

Table XIV, XVI.

In May 1944 gastroduodenitis. Gonorrhea 4—5 times (relapse?) 8 years ago. No complications. Has two children.

Status 18th July, 1946. Age 32.5.

Still dyspeptic disturbances, conveys the impression of being neurasthenic and absorbed by his disease. Shaves every second or third day.

Physical exam.: The examination shows eunuchoid body growth with large hands and feet. Body height: 187 cm. Height when sitting: 89.7 cm. Distance between fingertips: 193 cm. Weight: 71.7 kg. Profuse terminal hair. See also p. 148.

No. 113: Dystrophia adiposo-genitalis (sanata).

R.H. m.P. 3119/43, born on 25th December, 1931.

p. 141, Table XVII.

Diabetes, obesity and gout in the family. Weight at birth: 3750 gm. Weight at the age of six months: 8 kg. Has always been obese. Obesity increased during the last years. Did well at school. Physically energetical.

Physical exam. (1943): Adipose with typical "Fröhlich distribution". Genitalia very small. Beginning growth of pubic hair. Sella turcica: 12×8 square mm.

Treatment. Physex 1000 I.U.×25 (?) from October, 1943, to January, 1944, Physex 1000 I.U.×30 from August to December, 1944. Besides diet for reducing weight.

Physical exam. (9th January 1946): Obesity subsiding, particularly of the abdomen. Some deposits of fat of the mammae. A small amount of glandular tissue is felt in the mammae. The testes and penis normally developed.

Status 12th December, 1946. Age 15.0.

Pollutions during the last 6 to 12 months. Shaves once monthly.

Physical exam.: The voice deep, genitalia externa normal, downy barbae, profuse growht of terminal hair. See also p. 152.

No. 114: Impotentia coeundi.

R.H. m.P. 3244/46, born on 21st December, 1894.

p. 103, 108, 168, Fig. 9, Table XXIII.

Twenty-five years ago bubo. No inconvenience since. Has been married for many years. Has three children. Last three months lack of erection ability. Ejaculatio præcox. Libido normal.

Status 22nd July, 1946. Age 51.7.

Physical exam. Cicatrix in the left inguen. Genitalia externa, prostate and other somatic sex characters normal. Blood pressure 185/85. Wassermann's test negative. See also p. 166.

No. 115: Infantilismus primarius.

R.H. m.P. 3329/46, born on 1st March, 1930.

Table XVI.

The father's family of low stature. The father and mother small. Three brothers and sisters of normal height and two below the average. The maternal grandmother diabetes. Has had parotitis, without orchitis. Has always been small, but has, however, grown 13 cm during the last 12 months. Got on well at school.

Status 29th July, 1946. Age 16.4.

Physical exam.: Small, well-proportioned. Voice breaking. Genitalia externa normal. Prostate small, firm. Moderate pubic hair. No hirci, no barbae. Sella turcia: 10 × 6 square mm, nothing abnormal. Eye examination: Nothing abnormal. See also p. 148.

No. 116: Impotentia coeundi.

R.H. m.P. 2666/46, born on 19th June, 1894.

p. 97, 99, 105, 108, Fig. 6, 9, Table XXIII.

Suffers from polyarthritis urica. Has always had ejaculatio præcox. For the last 3 months no erection, only a single pollution. Libido unchanged.

Status 6th August, 1946. Age 52.2.

Physical exam.: Genitalia externa, prostate and other somatic sex characters normal. See also p. 166.

No. 119: Dystrophia adiposo-genitalis.

R.H. m.P. 1658/46, born on 2nd June, 1934.

p. 142, 197, 266, Fig. 24, Table IX, XVI, XXIV, XXVII.

Mother and mother's sister obese, are said to have had a low metabolic rate. Brother diabetes. The patient had parotitis at the age of 7, without orchitis. Has always been stout, particularly the last year. Did well at school.

Status 24th July, 1946. Age 12.1.

Physical exam.: Small and very obese, of diffuse distribution. The face diffusely congested. No striae coeruleae. Left testis nut-kernel-sized, right is not felt. Penis very small, ½ cm is free. Prostate cannot be palpated. Nothing to express. Blood pressure 115/85. Sella turcica 11 × 8 square mm, nothing abnormal. See also p. 148.

Concerning the later development of the somatic sex characters, see p. 227.

No. 121: Dystrophia adiposo-genitalis (sanata).

R.H. Dept. G. 755/46, born on 24th February, 1926.

Table XVII.

Father has diabetes. The patient had poliomyelitis in 1934. Walks only with difficulty since. In 1938 pneumonia. Increasing adipositas since 1936. In May-June, 1939, admitted to Dept. G. of the Rigshospital, treated with Physex 200 I.U. × 20 and thyroidin 200 units daily. Again hospitalized September, 1946, for dystrophia adiposo-genitalis. Growth of pubic hair began 3—4 years ago.

Status 16th September, 1946. Age 20.7.

Erection once daily. No ejaculation. Shaves two or three times weekly.

Physical exam.: Considerable, equally distributed adipositas, chiefly of the hips and nates. The face red in spots. On both hips red striae. Voice deep. The size of the testes at the lower limit of the normal. Profuse (normal)

pubes. No hirci. Barbae coarse. Sella turcica: Nothing abnormal. Basal metabolic rate: 95—95—91 per cent (after Plum). I.Q.: 92 per cent.
Renal hormone excretion, 1939: < 30 R.U. of gonadotropic, < 11 M.U. of oestrogenic and 2 C.U. of androgenic hormone per diem; 5th September, 1946: 50 M. U., 20—50 M. U. and 15 I. U., respectively. See also p. 152.

No. 122: Evolutio præcox.
R.H. Dept. G. 748/46, born on 19th March, 1933.
p. 73, Table IX, XVI.

Diabetes and adipositas in the family. His mother's brother possibly had dystrophia adiposogenitalis. The patient has not had parotitis. Weight at birth: 3.250 gm. Always vigorous, the tallest and stoutest boy in the class, but is no good pupil. Striking increase in weight since 1943, has grown considerably. Puberty set in medio 1946. His voice cracked in the spring of 1946. Does not shave.

Status 2nd September, 1946. Age 13.6.

Physical exam.: Equal distribution of fatty deposits. Striae distensae in the anterior axillary fold, downwards on the abdomen and the nates. Testes normal, full development of pubes, very scanty hirci. Small downy barbae.

Output of urine normal (1 litre). Basal metabolic rate: 77—81—70 per cent. (after Plum). Blood pressure 155/80—130/65. Sella turcica: Nothing abnormal. Eye examination: Nothing abnormal. Neurological examination: Nothing abnormal. Pyelogram: Nothing abnormal. See also p. 150.

No. 123: Infantilismus primarius.
R.H. m.P. 3424/46, born on 13th November, 1930.
p. 142, Fig. 24, Table XVI, XXIV, XXVII, XXIX.

The mother very small, 145 cm. A brother aged 21 years measures 160 cm only. The father and an adult sister and brother are of normal height. The patient was small at birth and has always been smaller than children of the same age.

Status 5th August, 1946. Age 15.9.

Physical exam.: Small and feeble; pubic hair very scanty, otherwise quite infantile, looks like an 11-year-old boy. Also genitals like those of a boy of 11 years. Sella 6×7 square mm, i.e. below the limit of the normal for his age group. See also p. 152.

Concerning the later development of the somatic sex characters, see p. 228.

No. 126: Infantilismus secundarius.
R.H. m.P. 3909/46, born on 16th October, 1927.
p. 142, 183, 196, Fig. 24, Table IX, XVI, XXIV, XXVII.

Parents, sisters and brothers of normal height. The patient is the eldest of six. Weight at birth: 3,750 gm. No diseases of childhood. The growth was normal until the age of 3 years, when after a traumatic injury to the head the rate of growth decreased. Eruption of the last milk tooth at 13. Has not arrived at puberty. Stools always normal; fatty or stinking stools have never been observed.

Status 31st August, 1946. Age 18.10.

Physical exam.: Face of castrate type, a mixture of infantile and senile traits. The psyche infantile, seems to be rather intelligent and lively. Voice infantile. Hair of the scalp profuse. Otherwise no terminal hair. The mammae prominent, are felt to be of rather firm consistency, without glandular tissue. Diffuse truncal obesity. Is well-proportioned. The thyroid gland is not felt with certainty. No bradycardia. Genitals quite infantile. Testes not palpable (states that descent can be produced now and then). The scrotum corresponds to that of a 3- or 4-year-old boy, but is, however, pigmented as in an adult. Blood pressure 110/70. Hb. 86 per cent. Erythroc. 4,86 mill. Index. 1.00. Basal metabolic rate 121—110 per cent. Sella turcica of natural shape and size, apparently covered.

Sugar tolerance test: Max. 0.182 after 80 min.
0.132 „ 150 „

Fat analysis of the faeces normal. X-ray examination of passage through small intestine shows enteritis suspicious of sprue. See also p. 148.

Concerning the later development of the somatic sex characters, see p. 229.

No. 127: Gynaecomastia in normal puberty.
R.H. m.P. 3790/46, born on 3rd March, 1933.
p. 140, 169, 170, Table XI, XVI.

Since the autumn of 1945 development of mammae.

Status 19th September, 1946. Age 13.6.

The voice has cracked. Does not yet shave.

Physical exam.: Rather firm bilateral mammary tissue, 5 cm in diameter. Testes large, pubes profuse, but sharply defined. Very scanty hirci, no barbae. Sella turcica: 11 × 10 suare mm, nothing abnormal. Biopsy of mamma shows fibrosis (gynaecomastia): — — dense connective tissue, poor in cells, — — a single lumen which is lined with one layer of tall columnar epithelium, but otherwise no glandular tissue. No signs of inflammation or formation of tomour. See also p. 148.

No. 128: Infantilismus secundarius.
R.H. Outpatients' Clinic of Dept. G. 294/46, born on 12th June, 1933.
p. 183, Fig. 24, Table IX, XVII, XXVII.

Bilateral cryptorchidism.

Treatment. Physex 500 I.U. × 10 from 11th February to 18th March, 1946. 18th May, 1946, Dept. C. of the Rigshospital: Orchidomobilisatio c. herniotomia inguinalis. Later: Right testis can not be palpated with certainty, left is situated in the middle of the inguinal canal.

Status 3rd October, 1946. Age 13.4.

Physical exam.: Voice breaking. Testes cannot be palpated. Prostate infantile. No growth of terminal hair. See also p. 150.

Concerning the later development of the somatic sex characters, see p. 230.

No. 130: Aspermatism.
R.H. m.P. 4643/46, born on 21st October, 1915.
p. 72, Table VII.

Parotitis during infancy. No venereal discase. Last five years gastritis. Pollutions from the age of 14 to 15 years to the age of 20, since never orgasm or ejaculation. Libido normal, erection normal, but of short duration. Shaves daily.

Status 24th October, 1946. Age 31.0

Physical exam.: Habitus normal. Size of testes at the lower limit of the normal. Prostate too small, of homogeneous, firm consistency. Terminal hair normal. Renal hormone excretion: 0-50 M.U. of gonadotropic, 5 I.U. of androgenic and 20 M.U. of oestrogenic hormone per diem.

No. 133: Hypometabolism. Dystrophia adiposo-genitalis.
R.H. Outpatients' Clinic of Dept. G. 433/45, born on 4th February, 1933.
p. 87, 90, 95, Fig. 5, Table VIII, XVII.

Applied on account of excessive obesity.

Physical exam. (January 1945): Enormous obesity, enlargement of the mammae. The femora obese, bluish red. Testes hazel-nut-sized, a few pubes.

Admitted to Dept. G of the Rigshospital, February to April, 1945. Diagnosis: Myxoedema, adipositas, bradycardia. Basal metabolic rate: 72—79 per cent, serum cholesterol 318—342 m%.

Treatment. Physex 13 injections (strength?) in February—March, 1944, 500 I.U. × 10 from December 1945 to March, 1946, and tabl. glandulae thyreoideae 200—400 U. Metabolism one month efter discontinuance of treatment with the tablets: 66—61 per cent.

Status 6th November, 1946. Age 13.9.

Physical exam.: Marked adipositas, particularly of the trunk. Face congested,

without striae coeruleae s. distensae. Voice infantile. Testes small, firm. Scanty growth of pubic hair, no hirci, no barbae. Sella turcica: 9×8 suare mm, nothing abnormal. Concentration of erythrocytes 5,65 mill. /cubic mm. See also p. 150.

No. 134: Dystrophia adiposo-genitalis.
R.H. m.P. 4952/46, born on 6th February, 1933.
p. 198, 268, Fig. 24, Table IX, XVI, XXIV, XXVII, XXIX.
Stout from birth. Has attented a school for backward children.
Status 7th November 1946. Age 13.9.
Physical exam.: Voice infantile. Typical "Fröhlich distribution" of the adipositas. Presence of striae distensae abd. and pernosis of the lower legs. Profuse fatty tissue in the mammae with scanty glandular tissue. Testes small. The prostate a little below average size. Moderate growth of pubic hair, but on a diminished area. Sella turcica: Nothing abnormal. See also p. 148.
Concerning the later development of the somatic sex characters, see p. 231.

No. 135: Sexually mature dwarf.
R.H. Outpatients' Clinic of Dept. G. 2237/46, born on 29th May, 1930.
p. 73, Table XVI.
Applied on account of being too small. Has always been smaller than boys of his own age.
Status 20th November, 1946. Age 16.6.
The voice cracked three months ago. Has shaved once weekly during the last month. Presumably no pollutions.
Physical exam.: Small, but well-proportioned. Testes rather small. Rather dense pubes on a diminished area. No hirci. Barbae downy. Sella turcica: 10×9 square mm, nothing abnormal. See also p. 150.

No. 136: Dystrophia adiposo-genitalis.
R.H. Dept. G 936/46, born on 14th December, 1932.
p. 145, 197, 198, Fig. 1 b, 24, Table IX, XVI, XXIV, XXVII, XXIX.
Some cases of adipositas in the father's family, also children who were obese during adolescense. The patient has always been stout, but his weight has especially increased during the last twelve months. At the same time he has become a little indolent. Eats normally.
Status 21st November, 1946. Age 13.11.
Physical exam.: Proportions infantile. Testes normal-sized, but soft. Slight adipositas with feminine hips, but no pronounced "Fröhlich distribution". Genitals infantile, prostate small, a little soft. Beginning pubes. No hirci, no barbae. Sella turcica: Nothing abnormal. Eye examination: Astigmatismus myopicus. See also p. 148.
Concerning the later development of the somatic sex characters, see p. 232.

No. 138: Adipositas of moderate degree.
R.H. Outpatients' Clinic of Dept. G 51/44, born on 24th June, 1931.
Table XV.
Has been very obese since infancy. Admitted to Dept. G of the Rigshospital in 1943 and in 1944 for dystrophia adiposo-genitalis.
Treatment. Physex 1500 I.U.×20 from 5th October, 1944, to 23rd November 1944, and 1500 I.U.×20 from 13th January to 30th October, 1945. Later a few injections at long intervals.
Status 28th November, 1946. Age 15.5.
Right testis descended 18 months ago.
Physical exam.: Facies of castrate type. Thick, slack, panniculus adiposus, particularly of the trunk. Right testis somewhat small, left not palpable, penis small, thin, with pointed glans; prostate small, flat. Pubes dense, but on a slightly diminished area. A few hirci, no barbae. See also p. 146.

No. 139: Pubertas praecox adrenalis.
R.H. Dept. G 1038/46, born on 25th Sept., 1943.
p. 93, 94, 156, Fig. 4, Table XVI.

At the age of 5 months rickets treated with cod-liver oil. Normal development until his sixth month, when he began to occupy himself with his genitals. At the same time the penis started growing. Later growth of pubic hair.

May, 1946: Penis 7 cm, pubes on an area of 1 cm at the radix of the penis. X-ray photo of the skull: Nothing abnormal. Sella turcica: Nothing abnormal. X-ray of kidney and pyelography: Nothing abnormal.

28th November: X-ray of the skull: Rather large. Theca not thin, not pronounced impressiones digitatae. The form almost rachitic. Sugar tolerance test: Normal. Blood pressure 110/60. Neurological examination: Not suspicious of intracranial tumour, e.g. pinealoma.

Status 21st November, 1946. Age 3.2.

Physical exam.: Acne faciei, the face looks like that of a 7-year-old boy. The psyche corresponds to the age. Testes nut-kernel-sized, penis long, thick. Pubes long, but rather scanty, only at the radix of the penis, no hirci, no barbae. Prostate just below the normal, but distinctly prominent, firm. Blood pressure 110/60.

Renal hormone excretion 2nd December, 1946: 0-50 M.U. of gonadotropic, 20 I.U. of androgenic and <20 M.U. of oestrogenic hormone, and 23rd December, 1946: 82 (photometrically) and 35 (biometrically) C.U. of androgenic hormone per diem, respectively.

Explorative operation through bilateral lumbar incision showed strongly hyperplastic suprarenal glands. See also p. 150.

No. 140: Impotentia coeundi.
R.H. m.P. 851/42, born on 23rd April, 1890.
Table XXIII.

Exophtalmic goitre 1941. Subtotal strumectomy in 1942. Before the operation coitus every second or third week, after the operation every or every second month or less. No ejaculation during the last 18 months. Has four children.

Status 3rd December, 1946. Age 56.8.

Physical exam.: Genitalia externa normal. Prostate somewhat large and firm; micturition unimpaired. The other somatic sex characters normal. See also p. 166.

No. 141: Infantilismus primarius.
R.H. Dept. G 1063/46, born on 3rd August, 1930.
Table XVI.

No familial predisposition, apart from the fact that his father is said to have developed late. At the age of 9 years a slight concussion, followed by headaches of long duration.

Obese, but otherwise well-proportioned until his 11th year, at which time his growth ceased; he has, however, grown again (4 cm) during the last 10 months. Admitted to the Medical Department of the Slagelse Hospital September—October, 1946 for dwarfism. Renal hormone excretion: 0-50 M.U. of gonadotropic, 5 I.U. of androgenic and <20 M.U. of oestrogenic hormone per diem. Basal metabolic rate: 90—92 per cent. Admitted to Department G. of the Rigshospital in December, 1946.

Status 19th December, 1946. Age 16.4.

Has only shaved a few times; for the first time nine months ago.

Physical exam.: Testes rather small. Prostate well-developed, of normal size and consistency. Rather dense pubic hair, but only on a limited area at the radix of the penis. Very scanty hirci. Barbae downy. Sella turcica: X-ray of intestinal passage: Nothing abnormal. See also p. 148.

No. 142: Hypoplasia testis.
R.H. m.P. 5494/46, born on 19th August, 1916.
p. 164, 165, Table XVI, XXII.

Puberty about the age of 13 years. No parotitis, no venereal disease. Has always been disposed to fall asleep in the daytime. Feels always sleepy. Exempted from military service on account of the adipositas. Ten years ago four attacks of influenza in rapid succession. In 1943 blood-poisoning following a carbuncle. Operated upon for gall-stones in November, 1946. Metabolism June, 1946: 73—75 per cent. Has wanted children of his own during four years, but had none. Sexual functions normal. Coitus two or three times weekly. Has always had small testes, never pain in the testes. Shaves every second day.

Status 12th December, 1946. Age 30.4.

Physical exam.: No myxoedematous features. Truncal fatness of "Fröhlich distribution". Presence of striae. Both testes very small, in the top of the scrotum. Left testis soft. Prostate normal. Profuse terminal hair. Barbae coarse. Examination of semen: Aspermia. Metabolism: 80—83. Biopsy of testes: Chief diagnosis: Atrophic testicular tissue (with hyalinization and proliferation of the Leydig cells). See also pages 150 and 164.

No. 144: Hypoplasia testis.
R.H. m.P. 158/47, born on 8th January, 1912.
p. 156, 164, 165, Table XVI, XXII.

Previously healthy. No parotitis. Wanted children for 18 months, but had none. Libido and potency normal. Coitus 3 to 4 times monthly. Shaves every or every second day. Examination of semen: Aspermia (2.7 ml, slightly tenacious).

Status 9th January, 1947. Age 35.0.

Physical exam.: No adipositas. Figure feminine. Broad hips, slender limbs. Muscles of small volume. No mammae. Testes very small, soft and flat. Prostate almost normal-sized, firm, rather prominent. Normal growth of terminal hair. See also pages 150 and 164.

No. 145: Infantilismus primarius.
R.H. m.P. 5366/46, born on 22nd July, 1931.
Table XV.

Hit father addicted to alcohol. A paternal aunt has had exophthalmic goitre. No dwarfs in the family. The patient is No. 3 of 8. At the age of 6 pneumonia, otherwise healthy. Of normal height and weight until his 8th year. Then too slow growth. Output of urine normal.

Status 16th January, 1947. Age 15.6.

Physical exam.: Is slender. Voice breaking. Testes somewhat small. Prostate small, almost infantile. Pubes at the radix of the penis, slight growth of anoperineal hair. Moderate hirci, no barbae. See also p. 146.

No. 149: Pubertas tarda.
R.H. m.P. 421/47, born on 8th August, 1929.
p. 87, 90, 142, 181, 196, 197, 266, Fig. 1 b, 24, Table VIII, IX, XVI, XXIV, XXVII.

No. 3 of 4 sisters and brothers. Operated upon for right-sided harelip. Wears prosthesis. Absence of libido. At rare intervals erections. Never ejaculation or pollution. Both testes in the scrotum, but the right is inclined to pass up.

Status 6th February, 1947. Age 17.6.

Physical exam.: Quite infantile. Is tall. Voice high. No obesity. No mammae. Testes very small. Prostate infantile, is scarcely felt. No growth of terminal hair. See also p. 148.

Concerning the later development of the somatic sex characters, see p. 233.

No. 151: Dystrophia adiposo-genitalis.
R.H. Outpatients' Clinic of Dept. G., 149/47. Born on 4th January, 1933.
p. 87, 142, 199, 264, 268, Fig. 1b, 24, Table VIII, IX, XVII, XXVII.

Ten injections of Physex (strength?) 1½—2 years ago for cryptorchidism. Has become stouter and more indolent during the last twelve months. Did well at school, but is wordblind. Appetite above the average.

Status 30th January, 1947. Age 14.1.

Physical exam.: Facies infantile. Typical dystrophia adiposo-genitalis with fatty breasts (no glandular tissue), fatty deposits on hips and downwards on the abdomen. Scrotum pendulous and thin-walled. Testes: Right testis in the middle of the scrotum, very small, but firm, left not palpable. Penis very thin and pointed and embedded in fat. Prostate is not palpated. Five or six scattered pubic hairs (appeared during Physex treatment). No hirci, no barbae, Sella turcica: Nothing abnormal. See also p. 150.

Concerning the later development of the somatic sex characters, see p. 234.

No. 153: Eunuchoidismus.
Private patient. Born on 1st December, 1912.
p. 69, 87, 90, 181, 254, 255, 259, 264, 265, Fig. 1 b, 24, Table VII, IX, XV, XXVII, XXX, XXXI.

Puberty did not set in, for which reason the patient has been treated since 1944 with Physex 1500 I.U. three times weekly. Temporary discontinuance from December, 1946, to January, 1947. Last injection 16 days ago. Throughout 1946 also treated with tabelttae glandulae thyreoideae 200 T.U. daily.

Status 20th February, 1947. Age 34.2.

Libido during treatment, disappears when not treated. During treatment, erection and ejaculation ability which also disappear when the Physex treatment is discontinued. Can practise coitus occasionally. Shaves once weekly, but barbae are quite soft. Terminal hair provoked by the treatments.

Physical exam.: Comparatively small, obese castrate type with high voice and slender limbs. No gynaecomastia. Testes too small and soft, penis small, thin and pointed. Prostate is not felt with certainty. Profuse pubes, but sharply defined, moderate hirci. Growth of body hair very scanty, but a certain, though small, growth of hair, along the linea alba. Barbae soft and scattered. See also p. 146.

Concerning the later development of the somatic sex characters, see p. 235.

No. 154: Infantilismus primarius.
R.H. m.P. 1023/44, born on 25th August, 1929.
Table VIII, IX, XVII.

No familial predisposition. I a twin. Until the age of 6 of normal size. after that time the other twin grew more rapidly, and is now about 20 to 25 cm taller than the patient.

Treatment. Physex, presumably 1500 I.U. × 10 × 2, latest in 1945.

Status 29th January, 1947. Age 17.5.

Physical exam.: The voice not breaking. Prostate small, but rather firm. Scanty pubic hair at the radix of the penis (appeared after discontinuance of Physex treatment). No hirci, no barbae. Basal metabolic rate: 96—99. See also p. 152.

No. 155: Infantilismus primarius.
R.H. m.P. 4310/45, born on 21st February, 1930.
Table XV.

No. 2 of 4. Maternal grandmother diabetes. Paternal grandfather small of stature. A sister and a brother are tall. A younger brother is small like the patient. The patient was of normal size until his 12th year, since then no body growth.

Treatment: Since October, 1945, treated with tablettae glandulae thyreoideae 100 T.U. daily, duration of treatment unknown.

Status 27th February 1947. Age 17.0.

Small and slender, infantile habitus. The size of the testes at the lower limit of the normal. Penis long, but thin. Prostate too small. Two or three pubic hairs at the radix of the penis, no hirci, no barbae. Sella turcica: 10 × 6 square mm, nothing abnormal. See also p. 146.

No. 156: Infantilismus primarius.

R.H. m.P. 1433/44, born on 10th August, 1929.

Table XVI.

No familial predisposition. No diseases of childhood. Has had rickets and enuresis nocturna. His voice cracked at the age of 14. Has always been small, but started growing and eating more 2 or 3 years ago. Is the smallest in his class.

Status 27th February, 1947. Age 17.6.

Physical exam.: Testes large, penis long and thick. Prostate small, but firm. Pubes dense, but cover only a limited area, no hair along the linea alba. No hirci, no barbae. Basal metabolic rate: 101—100 per cent. See also p. 150.

No. 159: Impotentia coeundi.

R.H. m.P. 814/47, born 28th January, 1900.

p. 146, Fig. 22, Table XXIII.

Gonorrhea at the age of 19 years. Traumatic injury to the penis during coitus in the spring of 1946. Since then always anxious during coitus with failing erection. Normal ejaculation, no ejaculatio præcox. Has two children

Status 27th February, 1947. Age 47.1.

Physical exam.: Apart from a right-sided spermatocele the genitalia externa, the prostate and the other somatic sexual characters are normal. See also p. 166.

No. 160: Infantilismus primarius.

R.H. m.P. 2066/44, born on 6th January, 1931.

Table XVII.

The youngest of three. The parents rather small. The patient had parotitis at the age of 11. Always small of stature. Genitals too small. The voice cracked about 2 years ago. Has never shaved. Basal metabolic rate (1944): 118—122.

Treatment. From May to October, 1944, Physex 1000 I.U. × 26.

Status 6th February, 1947. Age 16.1.

Physical exam.: Testes of normal size. Prostate smaller than the normal, but firm. Dense pubic hair, but sharply defined, without growth of hair along the linea alba. Rather profuse growth of anoperineal hair. A few hirci, beginning, downy barbae. See also p. 152.

No. 161: Impotentia coeundi.

R.H. m.P. 560/47, born 24th April, 1895.

Table XXIII.

Nervous, psychogenic headache during the last six months. In the same time failing erection, but normal libido and ejaculation ability.

Status 6th February, 1947. Age 51.10.

Physical exam.: Genitalia externa, prostate and other somatic sex characters normal. See also p. 166.

No. 162: Infantilismus secundarius.

R.H.m.P., born on 5th May, 1928.

Table XVI.

Since childhood suffered from a rather severe asthma bronchiale. Has always been a little smaller than boys of the same age. Puberty at the age of 15. Has only shaved once. No pollution or ejaculation.

Status 24th January, 1947. Age 18.8.

Physical exam.: The voice breaking. Testes normal, prostate somewhat smaller than the normal size. Pubes dense, but only covering a limited area. Rather profuse growth of anoperineal hair. Hirci normal, barbae downy. See also p. 148.

No. 163: Dystrophia adiposo-genitalis (sanata).
R.H. m.P. 847/47, born on 15th January, 1932.
p. 141, Table VIII, XIV, XVII, XXX.

In 1938 admitted to Dept. G of the Rigshospital for adipositas, cryptorchismus dxt., hypogenitalism. Nephritis haemorrhagica in 1944, since no albumen in urine.

Treatment. Low fat diet. Physex dose and duration unknown. No treatment during last 4 years.

Status 6th March, 1947. Age 15.2.

Physical exam.: Truncal adipositas, presence of striae coeruleae axillae et abdominis. Facies suspicious of Cushing's disease. No mammae. Testes large, prostate small, but not quite infantile. Moderate pubic hair, sharply defined. A few dispersed hirci. No barbae. Metabolism: 99—89 per cent. Fasting blood sugar: 0.116 m%. Output of urine: Normal. See also p. 152.

No. 164: Pubertas tarda.
R.H. m.P. 865/47, born on 26th February, 1928.
p. 73, 254, 255, 259, 261, 264, Fig. 24, Table IX, XVI, XXIV, XXVII, XXX, XXXI.

Has always been small. Somewhat mentally retarded. Morning erection during the last twelve months. No pollutions. Growth of pubes commenced 12 months ago. Shaving twice monthly during the last six months.

Status 27th February, 1947. Age 19.0.

Physical exam.: Castrate face. No mammae. Testes normal. Prostate is scarcely felt. Rather dense pubic hair, but only at the radix of the penis. No hirci. Barbae downy. See also p. 148.

Concerning the later development of the somatic sex characters, see p. 236.

No. 165: Eunuchodismus.
Private patient, born on 23rd October, 1910.
p. 69, 87, 90, 181, 254, 257, 261, 263, 264, 265, Fig. 1 b, 24, Table VII, IX, XVII, XXVII, XXX, XXXI.

Complaint: Deficient sexual maturation. Since December, 1938, received Physex (3000 I.U.), Antex (1500 I.U.) and testosterone propionate in large amounts. During the treatment, growth of terminal hair. Furthermore, potentia coeundi, which, however, disappears when the treatment is discontinued. Has married. Latest treatment (Physex) six weeks ago.

Status 20th March, 1947. Age 36.5.

No erections at present. Latest ejaculation 10 days ago. Shaves once weekly.

Physical exam.: Typical castrate face. Bilateral mammary tissue of macaroon-size. Testes too small. Prostate palpable, but is too small and flat. Density of pubic hair below normal, covering a limited area. Lack of virile stripe. Hirci normal. Barbae downy. See also p. 152.

Concerning the later development of the somatic sex characters, see p. 237.

No. 166: Infantilismus primarius.
R.H. m.P., born on 3rd September, 1928.
Table XVI.

The eldest of six. The parents of average height. None of his brothers and sisters are taller than the patient. Weight at birth: 4,500 gm.

Has had rickets at the age of 12 months. Growth of pubes commenced at the age of 14—15 years. His voice cracked at 16. Shaving once weekly for the last twelve months. In childhood of the same height as boys of his own age. Growth has ceased the last few years.

Status 20th March, 1947. Age 18.6.

Physical exam.: Voice deep. Testes large, prostate normal. Dense pubes, not sharply defined, but without hair along the linea alba. Presence of hirci. Barbae coarse. See also p. 148.

No. 167: Infantilismus primarius.

R.H. m.P. 2551/42, born on 6th March, 1928.

Table XVII.

No. 3 of four children. The parents of normal height. Paternal uncle diabetes. Paternal aunt very small, 3 sisters of normal height. The patient had scarlatina with nephritis at the age of 17 years. Was of the same height as his friends, until growth suddenly ceased for about a year. Started growing again after treatment. His voice broke at the age of 14 to 15.

Physical exam. (1942): No signs of puberty. Genitals like those of a 10 or 12-year-old boy. Body height 148.5 cm, height when sitting 70.5 cm, weight 37.1 kg. Blood pressure 145/80. X-ray of sella: 9×7 square mm., i.e. somewhat small. Renal hormone excretion: 30 R.U. of gonadotropic, 2 C.U. of androgenic and 20 M.U. of oestrogenic hormone per diem.

Treatment. Physex 1500 I.U.×28 from 27th October, 1942, to 19th February, 1943.

Status 27th March, 1947. Age 19.0.

Physical exam.: Testes large, prostate normal. Very dense pubes, but sharply defined. Moderate hirci. Downy barbae. See also p. 152.

No. 168: Eunuchoidismus.

Private patient, born on 28th November, 1929.

Table XVII.

Operated upon for bilateral cryptorchidism. Eunuchoid body growth.

Treatment. From the autumn of 1945 to the spring of 1946: Physex 500 I.U.×10 and 1500 I.U.×10. From December, 1946, to February, 1947: Perandren 5 mg×12 latest injection one week ago.

Status 2nd April, 1947. Age 17.5.

Physical exam.: Testes are not felt. Prostate too small, but palpable. Pubes profuse, rather diffuse, but no virile stripe. Moderate hirci, no barbae. See also p. 152.

No. 170: Infantilismus primarius.

R.H. m.P. 1101/47, born on 23rd February, 1932.

p. 87, 90, 142, 181, 183, 197, 254, 257, 264, 265, 266, Fig. 1 b, 24, Table VII, VII, IX, XVI, XXIV, XXVII, XXX, XXXI.

An only child. Not pubescent.

Status 15th March, 1947. Age 15.1.

Physical exam.: Quite infantile. No adipositas. Testes very small. Prostate small, infantile. No terminal hair. Sella 8×9 square mm. Basal metabolic rate: 96—102 per cent. See also p. 148.

Concerning the later development of the somatic sex characters, see p. 238.

No. 171: Infantilismus primarius (sanatus).

R.H. m.P. 2791/39, born on 18th March, 1926.

Table XVII.

The younger of two. Parents and sister of normal height. The patient had parotitis at the age of 7. Was of the same height as boys of his own age until he was 10 years old, at which time the growth ceased.

Treatment: Elityran, 2 tablets daily for periods from 1939 to 1941. October, 1941, to March, 1942: Physex 1000 I.U.×16 and 1500×5, March to October, 1942: 1500×40, October, 1942, to March, 1943: 1500 I.U.×2 weekly, April to July, 1944, Physex (dose unknown) and tablettae glandulae thyreoideae (dose unknown). From June, 1944, to the spring of 1946: Physex (dose unknown).

Physical exam. (1942): 11th March, 1942: Renal hormone excretion < 30 R.U.

of gonadotropic, 0 C.U. of androgenic and < 20 M.U. of oestrogenic hormone per diem. Blood pressure: 120/70. Onset of puberty at normal time. The patient began to shave at the age of 18, during the last 18 months 2 or 3 times weekly, but only along the ramus mandibulae.

Status 17th April, 1947. Age 21.1.

Libido normal. Has had a single pollution.

Physical exam.: Testes large, prostate normal. Profuse growth of pubic hair, not sharply defined, with slight growth of hair along the linea alba. Profuse growth of anoperinal hair. Presence of hirci. See also p. 152.

No. 172: Pubertas tarda.

R.H. m.P. 1002/46, born on 20th December, 1929.

p. 142, Table XVI.

The youngest of three. His father tall and vigorous. His mother 154 cm. Brother of the same height as the patient when he was of his age, now tall. Sister of normal stature. The patient has always been small, the smallest in the class. Dentition at normal time. Has had concussion of the brain twice, at 7 and 8. From his 7th to his 16th year suffered much from headaches. Blood pressure 125/75 (1946).

Status 17th April, 1947. Age 17.4.

Physical exam.: Well-proportioned. State of nutrition medium. Psychically infantile. The voice high. Testes large. Prostate infantile. Slight growth of lanugo pubes. No hirci, no barbae. See also p. 148.

No. 173: Dystrophia adiposo-genitalis (sanata).

R.H. m.P. 1760/39, born on 27th October, 1932.

Table XVI.

No familial predisposition. Has been weak with frequent attacks of fever and otitis during his first years. Increasing obesity since the age of 3 years. Descensus testis is said to have been retarded. Testes now in the scrotum.

Physical exam. (June 1939): Testes bean-sized. Penis very small. Basal metabolic rate 108—100 per cent. Eye examination: Nothing abnormal. Sella turcica: Normal. Renal hormone excretion: 30 R.U. gonadotropic, 0 C.U. of androgenic and 17 M.U. of oestrogenic hormone per diem.

Status 14th April, 1947. Age 14.6.

In well-being, is teased because of his adipositas.

Physical exam.: Diffuse adipositas, profuse striae coeruleae at the loins and in the arm-pits. Presence of mammary glandular tissue. Testes large. Prostate normal. Profuse growth of pubic hair, but sharply defined. Presence of hirci, no barbae. Basal metabolic rate: 117—113 per cent. Serum cholesterol 304 mg per cent. Sella turcica: Normal. See also p. 150.

No. 174: Dystrophia adiposo-genitalis.

R.H. m.P. 1463/47, born on 15th December, 1934.

p. 86, 142, 183, 254, 257, 259, 261, 263, Fig. 1 a, Table VII, IX, XVI, XXIV, XXX, XXXI.

Obesity in the family. Both parents, however, small and lean. The patient has had parotitis. Considerable increase in weight during the last four years. Urination every second hour.

Status 17th April, 1947. Age 12.4.

Physical exam.: Typical "Fröhlich adipositas"; presence of mammary glandular tissue. Right testis is not felt, left pea-sized. Penis very small, pointed. Prostate infantile. No terminal hair. Output of urine normal, about 1 litre. Eye examination: Normal conditions, apart from amblyopia cong. dxt. See also p. 148.

No. 176: Dystrophia adiposo-genitalis (sanata).

R.H. m.P. 1096/40, born on 16th May, 1926.

Table XVII.

A few cases of adipositas in the family. The patient has always been a

little stout and his appetite above the average. From the autumn of 1939 to the spring of 1940 increased his weight by 12 kg.

Physical exam. (1940): Typical severe case of dystrophia adiposo-genitalis. Erythema pernio on the lower extremities. Genitals minimal, penis is only a "fold of skin". Testes hardly pea-sized, situated in the inguinal canal. Sella turcica normal. Basal metabolic rate: 100—96 per cent. Renal hormone excretion: 30 R.U. of gonadotropic, 2 C.U. of androgenic and 20 M.U. of oestrogenic hormone per diem.

Treatment. Many Physex injections (number unknown) with excellent effect.

Status 24th April, 1947. Age 20.11.

Shaves every second day.

Physical exam.: Appearance normal. The size of the testes at the lower limit of the normal. Penis long and thick. Pubes fully developed. Presence of hirci, barbae coarse. See also p. 152.

No. 178: Impotentia coeundi.
R.H. m.P. 1677/47, born on 18th June, 1910.
Table XXIII.

Denies venereal disease. During the last few years increasing impotentia erigendi. Orgasm normal.

Status 8th May, 1947. Age 36.11.

Physical exam.: Genitalia externa, prostate and other somatic sex characters normal. See also p. 166.

No. 179: Hypoplasia testis.
R.H. m.P. 1872/47, born on 24th July, 1887.
p. 164, Table XVI, XXII.

No parotitis, no orchitis. Uncomplicated gonorrhea in February, 1947, treated with tablets. Onset of puberty at the age of 16 or 17 years. Libido and potency normal. Shaves every second day. Has one child.

Status 8th May, 1947. Age 59.10.

Physical exam.: Both testes somewhat small and very soft. Prostate normal. Hernia inguinalis dxt. Terminal hair normal. See also pages 148 and 164.

No. 180: Myxoedema. Gonorrhea antea. Lues vetus.
The Blegdams Hospital, born on 6th April, 1904.
p. 95, Fig. 5.

Gonorrhea in 1935. Gonorrhea and syphilis in 1937, treated with injections. Eighteen months ago the patient commenced to increase his weight and to get tired. Basal metabolic rate 17th May, 1947: 67 per cent.

Status 8th May, 1947. Age 43.1.

Physical exam.: Myxoedematous habitus, Testes rather small, pigeon-egg-sized, soft. Prostate normal. Pubes, hirci and barbae normal.

No. 181: Impotentia coeundi.
R.H. m.P. 2876/33, born on 24th December, 1900.
Table XXIII.

Denies venereal disease. Impotentia coeundi for the last 6 years. Slight nervous depression.

Status 29th May, 1947. Age 46.5.

Physical exam.: Genitalia externa, prostate and other somatic sex characters normal. Blood pressure 160/110. See also p. 166.

No. 182: Impotentia coeundi.
R.H. m.P. 1294/47, born on 14th September, 1913.
Table XXIII.

Denies venereal disease. Impotentia coeundi since November, 1946.
Status 19th June, 1947. Age 33.9.
Physical exam.: Genitalia externa, prostate and other somatic sex characters normal. Basal metabolic rate 92—124 per cent. Blood pressure 170/110—155/100 —170/110. See also p. 166.

No. 184: Impotentia coeundi.
Private patient, born on 8th September, 1898.
p. 108, Fig. 9, Table XXIII.
In 1924 gonorrheal prostatitis. Now no complaints. During the last 10 years lack of libido. Coitus every second month only, with failing erection. No ejaculatio præcox.
Status 24th July, 1947. Age 48.10.
Physical exam.: Prostate slightly modular. Gentalia externa and other somatic sex characters normal. See also p. 166.

No. 186: Dystrophia adiposo-genitalis.
R.H. Dept. G. 519/46—789/47, born on 24th June, 1934.
Table XV.
No. 2 of 3 children. Parents, brother and sister healthy. A maternal aunt somewhat adipose. Birth normal. Weight at birth 3,500 to 4,000 gb. Since 1944 adipositas to an increasing degree.
Treatment. Injections (preparation unknown) for 10 days in May 1946.
Status 20th September, 1947. Age 13.3.
Physical exam.: Voice infantile. Pronounced adipositas of the "Fröhlich type". Marked gynaecomastia; no striae. Testes normal, prostate is felt, but is too small. Moderate pubic hair at the radix of the penis, beginning hirci. No barbae. Eye examination: Hypermetropia, no hemianopsia. Basal metabolic rate: 87—96 per cent. (according to weight), 122—134 per cent. (according to ideal weight). See also p. 146.

No. 187: Gynaecomastia in normal puberty.
Private patient, born on 26th September, 1933.
p. 140, 169, 170, Fig. 22, Table XI, XVI.
Since June, 1947, swelling of the left breast. Since September, 1947, also of the right.
Status 2nd October, 1947. Age 14.1.
Physical exam.: The voice in process of breaking. Right mamma: 90 Glandular tissue 21 mm in diameter. Left mamma: Glandular tissue 20 mm in diameter. Testes normal. Prostate of almost normal size, rather firm. Scattered pubic hair at the radix of the penis. No anoperineal hair. No hirci, no barbae. See also p. 148.

No. 188: Infantilismus primarius.
R.H. m.P. 1442/43, born on 14th June, 1928.
Table XVI.
Puberty at the age of 15. Commenced shaving three months ago, has shaved 3 or 4 times in all. Applied owing to too small growth.
Status 6th November, 1947. Age 19.5.
Physical exam.: Too small, but well-proportioned. The voice deep. Testes large; dense, fully developed pubes, but no growth of hair along the linea alba. Moderate hirci. Barbae rather coarse. See also p. 150.

No. 189: Infantilismus primarius.
Private patient, born on 24th February, 1927.
p. 159, Table IX, XVII, XXVII.
Puberty had not occurred at the age of 17; the patient wos also too small.

Treatment: In 1944 Physex 1500 I.U. alternating with Antex 1500 I.U., in all 100 injections. From December, 1946, to February, 1947: Physex 1500 I.U. 2 to 3 times weekly. From the middle of September to 2nd November, 1947, Physex 1500 I.U., total 20 to 30. For the last few months also tablettae glandulae thyreoidea 300 T.U. daily. About New Year, 1947, the pubes started growing, and downy barbae appeared.

Status 6th November, 1947. Age 20.9.

Physical exam.: Some diffuse truncal obesity. No mammary glandular tissue. The size of the testes at the lower limit of the normal. Dense pubes, but only covering a considerably decreased area. No hirci. Barbae, but only as a downy moustache. See also p. 152.

Concerning the later development of the somatic sex characters, see p. 239.

No. 190: Infantilismus primarius.

3967/47, born 6th August, 1932.

p. 142, Table XVI.

The younger of two. His brother normally developed. The patient has always been small and retarded in development. Did not manage well at school.

Status 13th November, 1947. Age 15.3.

Physical exam.: Quite infantile. Testes too small. Prostate almost infantile. Basal metabolic rate: 91—99 per cent. Sella turcica: Nothing abnormal. See also p. 148.

No. 191: Pubertas tarda.

R.H. m P. 4265/47, born on 10th October, 1931.

p. 142, 197, 264, 266, Fig. 24, Table IX, XVI, XXIV, XXVII.

The eldest of three. Operated upon for right-sided inguinal hernia. Is not strikingly small as compared with his comrades, but has grown less during the last few years. He thinks that the development of his genitals is retarded.

Status 4th December, 1947. Age 16.2.

Physical exam.: Penis pointed. Testes small. Prostate infantile, not palpable. One pubic hair. Otherwise no terminal hair. See also p. 148.

Concerning the later development of the somatic sex characters, see p. 240.

No. 192: Infantilismus secundarius.

R.H. m.P. 395/48, born on 7th October, 1932.

p. 142, 197, 254, 259, 261, 264, 266, Fig. 24, Table IX, XVI, XXIV, XXVII, XXX, XXXI.

No familial predisposition. Normal birth, but asphyctic and slack. Did not begin to walk and talk until the age of 4 or 5 years. Dentition when? Attends a class for backward children. Still talks and walks only with difficulty, spastic. The intelligence quotient found to vary from 80—100. Is always nervous and crying when confronted with something new. At the age of 12 months admitted to Dept. G. of the Rigshospital for fraenulum linguae and bad nervous system, and at the age of 3 years on account of "sluggishness". At the age of 9 in the Neuro-Medical Department of the Rigshospital for a nervous disease.

Status 8th January, 1948. Age 15.3.

Physical exam.: Infantile. Testes the size of green walnuts. Prostate not palpable. Only lanugo pubes. No hirci, no barbae. See also p. 148.

Concerning the later development of the somatic sex characters, see p. 241.

No. 193: Dystrophia adiposo-genitalis.

R.H. Outpatients' Clinic of Dept. G. 1927/46, born on 10th March, 1936.

p. 142, 192, 197, 266, Fig. 24, Table IX, XVI, XXIV, XXVII.

Applied on account of obesity.
Status 26th February, 1948. Age 11.11.

Physical exam.: Typical "Fröhlich distribution" of the fat. Presence of fatty mammae, no glandular tissue to palpate. Penis hardly visible, covered by fat. Testes pea-sized, prostate not palpable. No terminal hair. See also p. 148.

Concerning the later development of the somatic sex characters, see p. 243.

No. 194: Infantilismus primarius.
R.H. m.P. 815/48, born on 29th August, 1929.
p. 142, 196, 266, Fig. 24, Table IX, XVI, XXIV, XXVII.

Like the patient the father is said to have had unilateral cryptorchidism, but was spontaneously relieved. The patient is the youngest of seven brothers and sisters. One brother suffers from bilateral cryptorchidism, is of normal height. It is unknown if the patient has always been small, or if growth has ceased during childhood. Wants treatment for dwarfism and absence of puberty.
Status 4th March, 1948. Age 18.7.

Physical exam.: Small and slender, the neck a little short. Hutchinson's teeth. Testes: Left very small, right a little larger, palpable in the annulus inguinalis. Penis quite infantile. Prostate is not felt. No growth of terminal hair. Sella turcica 4×4 square mm, i.e. considerably diminished. Wassermann reaction negative. See also p. 148.

Concerning the later development of the somatic sex characters, see p. 243.

No. 195: Eunuchoidismus.
Private patient, born on 29th May, 1929.
Table XVII.

No familial predisposition. Is the eldest of eleven. Applied in 1943 on account of too small testes.

Treatment. Physex 1500 I.U. (how many?) for six months in 1943. Hereafter growth of pubic hair and breaking of voice, erection and ejaculation ability.
Status 4th March, 1948. Age 18.10.
Has shaved 5 times in all during the last six months. The beard consists of a downy moustache.

Physical exam.: Rather long, with eunuchoid proportions. Testes very small and soft; in the left half of the scrotum ample epididymal(?) tissue is felt. Penis long, somewhat thin. Prostate a little diminished, firm. Rather dense pubes, but only covering a reduced area. Moderate hirci. See also p. 152.

No. 196: Infantilismus primarius.
R.H. Outpatients' Clinic of Dept. G. 188a/48, born on 13th September, 1934.
p. 142, 196, 266, Fig. 24, Table IX, XVI, XXIV, XXVII.

His mother and maternal grandparents small, but not dwarfs. The patient is an only child. During infancy often ill, had pneumonia three times. In good health during the last few years. Has always been smaller than children of the same age. Stammers and does not do well at school.
Status 18th March, 1948. Age 13.6.

Physical exam.: Extremities comparatively short, the head somewhat large, but not hydrocephalic. Slight obesity. Testes nut-kernel-sized, penis small and thin. No terminal hair. Basal metabolic rate 111—96 per cent. Sella turcica normal shape, 8×9 square mm. See also p. 148.

Concerning the later development of the somatic sex characters, see p. 244.

No. 199: Infantilismus primarius.
R.H. Dept. G. 382/48, born on 23rd February, 1932.
Table XVI.

His father of normal height. His mother 149 cm. His mother's family are small. A sister of 14 years is 158 cm tall. The patient is the eldest of five.

Scarlatina with nephritis at the age of 5 years, now no proteinuria, normal urine microscopy. Has always been the smallest among his comrades.
Status 2nd April, 1948. Age 16.2.

Physical exam.: Small, but well-proportioned. Testes of normal size for his age, prostate palpable, but very small. Beginning pubes, no hirci, no barbae. Eye examination: Nothing abnormal. See also p. 148.

No. 250: Eunuchoidismus.
R.H. m.P. 1492/48, born on 22nd September, 1920.
p. 156, Table XVI.

Rickets during childhood. No parotitis. No hair on the scalp until his fifth year, since then normal capillitium. As a child of normal stature, but lean. After his 14th year increased growth of body and extremities. Pubes not until his 17th year. Began shaving about his 17th year, at the beginning once weekly, but has now stopped again. Presence of libido and erection ability, but very seldom orgasm. Till now he has had about 20 ejaculations, all of a small volume.
Status 27th April, 1948. Age 27.7.

Physical exam.: Pronounced eunuchoid. Body height 183.9, span 182 cm, height when sitting 85 cm. Testes pea-sized, penis long, but rather thin, prostate a little under normal size. Rather dense pubes, but only covering a very diminished area. Presence of hirci, no barbae. Sella turcica 10×8 square mm. See also p. 150.

No. 251: Eunuchoidismus.
R.H. Dept. G. 3077/47, born on 27th May, 1930.
Table XVII.

No familial predisposition apart from the fact that his mother is suffering from diabetes (occurred after the patient's birth). The patient is No. 3 of 5. Weight at birth 4,000 gm. Rickets at the age of 2. In 1938 operated upon for appendicitis and peritonitis. Applied on account of cryptorchidism and absence of puberty.

Treatment. Physex 1500 I.U. $\times 2$ weekly, total 50 until August, 1947, 1500×24 from September to December, 1947, and 1500×16 from January to March, 1948.

Physical exam. (August 1947): Eunuchoid habitus, scanty pubes. Eye examination: Nothing abnormal. Sella turcica: Nothing abnormal. 14th August, 1948, right-sided incisio explorativa: After incision of the tunica vaginalis is found a small blastema chiefly consisting of epididymis. A real testicular blastema is not visible at all, but a well-developed vas deferens is felt, extending right down to the region. On the left side conditions are felt to be quite identical with those on the right side.
Status 25th August, 1948. Age 18.3.

Physical exam.: Slightly eunuchoid proportions. Abdomen a little obese. The voice infantile. Scrotum small, empty, penis small and thin. Prostate almost infantile, is hardly felt. Pubic hair shaved, no hirci, no barbae. Body height 161 cm, span 163 cm, height when sitting 78.5 cm. Weight 56 kg. See also p. 150.

No. 302: Dystrophia adiposo-genitalis (sanata).
Private patient.
Table XVII.

In 1934 dystrophia adiposo-genitalis and decreased libido were ascertained. Received 5 mg of methyl testosterone daily, last time a month ago.
Status 12th March, 1946. Age 37.0.

Libido normal, shaves daily.

Physical exam.: Still rather obese. No mammae. Genitalia externa, prostate and other somatic sex characters normal. See also p. 152.

No. 303: Infantilismus primarius.
Private patient, born on 2nd September, 1928.
Table XV.

Physical exam. (January 1946): Small, well-proportioned. Genitalia correspond to those of a 14-year-old boy. A few pubes, no hirci, no barbae.

Status 14th March, 1946. Age 17.6.

Physical exam.: Unchanged. Testes rather large. Penis not quite infantile. See also p. 146.

No. 304: Infantilismus primarius.
Private patient.
Table XV.

Treatment one year ago with 30 Physex injections for nanism. Hereafter onset of puberty.

Staaus 13th March, 1946, Age 20.7.

Physical exam.: Infantile habitus. Voice breaking. Testes rather large. Pubes moderate, scanty growth of anoperineal hair. No hirci, no barbae. See also p. 146.

No. 305: Infantilismus primarius.
Private patient, born on 21st August, 1925.
Table XVI.

Treated for small growth and absence of puberty with Phyol and tablettae glandulae thyreoideae, after which he arrived at puberty. Is still being treated.

Status 13th March, 1946. Age 20.7.

Pollution once weekly. Libido normal, presence of ejaculation ability.

Physical exam.: Varicocele sin. Genitalia externa, pubic hair and hirci normal. See also p. 148.

No. 306: Pubertas tarda (sanata).
Private patient.
Table XVII.

Treated with Physex for absence of puberty, after which puberty occurred at the age of 17. Discontinuance of treatment September, 1945. Is a transvestite.

Status 14th March, 1946. Age 25 years.

Ejaculation once weekly. Shaves two or three times weekly.

Physical exam.: Genitalia externa, prostate and other somatic sex characters normal. See also p. 154.

No. 308: Eunuchoidismus (sanatus).
Private patient.
Table XVII.

Treated in 1941 with methyl testosterone for eunuchoid habitus.

Status 13th March, 1946. Age 35 years.

Libido weak. Sensation of muscular asthenia.

Physical exam.: Is lean, gracile, with poorly developed musculature, but not eunuchoid. Genitialia externa, prostate and other somatic sex characters normal See also p. 152.

No. 309: Pubertas tarda (sanata).
Private patient.
Table XVII.

Onset of puberty about the age of 16 years. Complaints: Lacking ejaculation at coitus, though ejaculation at masturbation. A few pollutions. Treated with Physex.

Status 6th April, 1946. Age 26 years.

Shaves every or every second day.

Physical exam.: Varicocele sin. Prostate strikingly soft and small. Testes of normal size. Terminal hair fully virile. See also p. 152.

No. 310: Dystrophia adiposo-genitalis (sanata).
Private patient, born on 16th Juli, 1928.
Table XVII.

Treated with Physex since September, 1941, for dystrophia adiposo-genitalis, latest injection over twelve months ago. Puberty set in during the treatment.

Status 21st March, 1946. Age 17.8.

Libido normal. Presence of pollutions. Does not shave.

Physical exam.: Testes normal, penis very small and thin. Very rich growth of pubic hair, not sharply defined. Hirci normal, barbae scanty, downy. See also p. 152.

No. 311: Eunuchoidismus.
Private patient, born on 20th November, 1917.
p. 73, Table XVII.

On account of too faint puberty (December, 1945, only scanty pubes and a few hirci, but no barbae) treated with Physex 1500 I.U. twice weekly from 14th December, 1945, to 7th March, 1946. Downy barbae appeared during the treatment.

Status 19th March, 1946. Age 28.4.

Shaves once weekly. A single pollution during the Physex treatment. Ejaculation twice monthly.

Physical exam.: Obesity of "Fröhlich distribution", castrate face. Rather vigorous fatty mammae. The voice is breaking. Testes somewhat small, but within the limits of the normal. Prostate normal, pubes moderate. No hirci, barbae downy. See also p. 152.

No. 312: Infantilismus.
Private patient, born on 19th May 1931.
Table XV.

Applied in 1943 owing to too small growth of the testes.

Physical exam. (April 1943): Is infantile, not obese. Right testis nut-kernel-sized, left not palpable.

Treatment. Physex from April, 1943, to the summer of 1944 with good effect.

Physical exam. (January 1946): The genitals correspond to the age. Scanty hirci and barbae.

Status 26th March, 1946. Age 14.10.

No ejaculation.

Physical exam.: Breaking of voice. Testes rather large. Beginning pubic hair. Now no hirci. No barbae, but a few downs. See also p. 146.

No. 314: Eunuchoidismus (sanatus).
Private patient.
Table XVII.

Treated with Physex and testosterone propionate once weekly until November, 1939, for lacking puberty.

Status 4th April, 1946. Age 24 years.

Coitus every third or fourth day. Shaves daily.

Physical exam.: Is very long, with eunuchoid proportions. Large varicocele on both sides, particularly the left. Both testes rather firm, left a little small. Prostate normal. Profuse growth of terminal hair. See also p. 154

No. 315: Dystrophia adiposo-genitalis.
Private patient, born on 1st May, 1932.
Table XVII.

In July, 1943, commenced Physex treatment for dystrophia adiposo-genitalis.

Status 8th August, 1946. Age 14.3.

Presence of erections, absence of pollutions.

Physical exam.: The voice in process of breaking. Testes normal, right in the middle, left at the bottom, of the scrotum. Pubic hair dense, but sharply defined. No hirci, no barbae. See also p. 152.

No. 316: Hypoplasia testis.

Private patient.

Table XVII, XXII.

Parotitis at the age of 14 years. No orchitis. Jaundice three or four years ago. Puberty about the age of 14 to 15 . Coitus two or three times weekly. Shaving two or three times weekly, barbae coarse. Complaint: Infertility. Has wanted children of his own for 3 years. Examination of semen showed aspermia.

Treatment. Physex 1500 I.U. one injection 24th September, 1946.

Status 30th August, 1946. Age 31 years.

Physical exam.: Rather small. Slightly diffuse adipositas. Testes small and very soft. Terminal hair fully virile. See also pages 152 and 164.

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"0"	—	5	2	—	3	3	1 —	—	—	2	2	1	1 1	4	2	1	—	—	—
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1 - <5	—	1	3	—	—	—	3 1	—	—	—	—	—	— 4	—	—	2	2	—	—
5 - <10	—	1	1	—	—	—	2 —	—	—	—	—	—	— 2	—	—	1	—	—	1
≥10	—	—	3	—	—	—	1 3	—	—	—	—	1	— 3	—	—	—	1	2	—

Table XIX

The Individuals of the Various Groups, distributed according to Concentration of Phosphatase and the other Sex Characters (see also Tables XVI, XVII and XVIII).

Terminal Hair					Prostate					Appearance of expressed secretion				Androgenuria (biometrical)			Ages					
0	1	2	3	4	0	1	2	3	4	1	2	3	4	10	20	30	<11	11	12	13	14	1
d. cf. Table XVI.																						
16	2	—	—	—	13	4	—	—	—					5	—	—	—	1	3	2	1	4
1	7	2	1	—	—	5	2	—	1	9	2	—	—	2	1	—	—	—	—	3	2	1
1	2	1	3	—	—	1	1	—	3	—	4	1	2	3	—	—	—	—	1	—	1	—
—	3	3	1	5	—	1	5	1	2	—	—	3	7	1	2	1	2	—	—	1	1	
—	3	5	3	8	—	—	4	—	14	—	—	5	15	2	3	3	2	1	—	—	1	1	—
Untreated.																						
6	1	—	—	—	4	2	—	—	—					2	—	—	—	—	—	1	1	
1	2	—	1	—	—	2	—	—	1	3	1	—	—	—	—	—	—	—	—	—	1	—
—	—	—	1	—	—	—	—	—	1	—	1	—	—	1	—	—	—	—	—	—	—	—
—	1	—	—	—	—	—	1	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—
—	1	1	1	—	—	—	1	—	2	—	—	1	2	—	1	1	—	—	—	—	—	—
us. Untreated.																						
3	—	—	—	—	3	—	—	—	—					1	—	—	—	—	—	—	—	
—	1	—	—	—	—	—	—	—	—	1	—	—	—	—	1	—	—	—	—	—	—	—
—	1	—	—	—	—	—	—	—	—	—	1	—	—	1	—	—	—	—	—	—	—	—
—	—	1	—	—	—	—	1	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
oidismus. Untreated.																						
2	1	—	—	—	2	1	—	—	—					1	—	—	—	—	—	—	—	
—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	1	—	—	1	—	—	—	—	—	1	—	1	—	—	—	—	—	—	—	—
—	—	1	—	—	—	—	1	—	—	—	—	1	—	—	1	—	—	—	—	—	—	—
—	—	1	—	—	—	—	1	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—
alis. Untreated.																						
5	—	—	—	—	4	1	—	—	—					1	—	—	—	1	3	1	—	
—	3	2	—	—	—	2	2	—	—	4	1	—	—	2	—	—	—	—	—	2	1	
1	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	1	—	—	
—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	
—	—	1	—	—	—	—	—	—	1	—	—	—	1	—	—	—	—	—	—	—	1	
viduals. Untreated.																						
—	1	—	—	—	—	1	—	—	—	1	—	—	—	—	—	—	—	—	—	1	—	
—	1	1	1	—	—	—	1	—	2	—	2	—	1	—	—	—	—	—	—	—	1	
—	2	1	1	—	—	1	1	—	1	—	—	2	2	1	1	—	—	—	—	1	1	
—	1	1	1	—	—	—	1	—	2	—	—	1	3	—	—	—	—	—	—	—	—	
cf. Table XVII.																						
—	4	1	—	—	3	2	—	—	—					4	—	—	1	—	—	—	—	1
1	4	1	—	—	—	5	1	—	—	5	—	—	—	—	1	—	—	—	—	—	2	—
—	—	2	1	1	—	—	3	—	—	—	2	2	1	1	—	—	—	—	—	—	—	1
—	3	4	5	3	—	—	6	1	4	—	—	9	3	—	—	1	1	—	—	—	—	—
—	1	3	3	14	—	—	4	1	11	—	—	—	19	1	2	—	1	—	—	1	—	1
alis. Untreated.																						
6	1	—	—	—	3	4	—	—	—								—	—	—	1	6	
1	2	2	—	—	—	3	2	—	—	2	2	1	—				—	—	—	2	2	
—	3	1	—	—	—	2	2	—	—	—	2	2	—				—	—	1	—	1	
—	1	1	—	—	—	—	1	—	1	—	—	1	1				—	—	—	1	—	
—	2	2	—	—	—	—	4	—	—	—	—	1	3				—	—	—	1	1	

				Carpal Age										Age of patients with carpal age determined									
5	16	17	≧18	<11	11	12	13	14	15	16	17	≧18		<11	11	12	13	14	15	16	17	≧18	
: 2	2	3		1	3	5	—	—	1	—	—	—		—	—	2	1	1	2	1	1	2	
[4	—	1		—	1	1	3	2	—	1	—	—		—	—	—	2	2	—	3	—	1	
– 3	1	2		—	2	1	—	—	—	—	—	—		—	—	1	—	—	—	1	1	—	
[1	—	8		—	—	—	1	1	—	1	1	2		—	—	—	1	—	—	1	—	4	
– 4	2	12		1	—	—	—	2	—	1	—	4		1	—	—	1	—	—	—	1	5	
3 1	—	1		1	2	2	—	—	1	—	—	—											
– 2	—	1		—	1	—	3	—	—	1	—	—											
– 1	—	1		—	1	—	—	—	—	—	—	—											
– 1	—	—		—	—	—	—	1	—	—	—	—											
— —	1	2		—	—	—	—	1	—	1	—	1											
1 —	—	2		—	1	1	—	—	—	—	—	—											
1 —	—	—		—	—	—	—	—	—	—	—	—											
— —	1	—		—	—	1	—	—	—	—	—	—											
— —	—	1		—	—	—	—	—	—	—	1	—											
— —	—	—		—	—	—	—	—	—	—	—	—											
— 1	2	—		—	—	1	—	—	—	—	—	—											
— —	—	—		—	—	—	—	—	—	—	—	—											
— —	—	1		—	—	—	—	—	—	—	—	—											
— —	—	1		—	—	—	—	—	—	—	—	—											
— —	—	1		—	—	—	—	—	—	—	—	—											
—	—	—	—	1	—	1	—	—	—	—	—	—											
—	2	—	—	—	—	1	1	2	—	—	—	—											
— —	—	—	—	—	1	—	—	—	—	—	—	—											
— —	—	—	—	—	—	—	—	—	—	—	—	—											
— —	—	—	—	—	—	—	—	—	—	—	—	—											
—	—	—	—	—	—	—	—	—	—	—	—	—											
—	2	—	—	—	—	—	—	—	—	—	—	—											
1	—	—	1	—	—	—	1	—	—	—	—	1											
—	3	1	1	—	—	—	—	—	—	—	—	—											
—	1	—	3	—	—	—	1	1	—	—	—	—		—	—	—	—	—	—	—	1	—	1
—	1	—	3	—	—	—	—	—	1	—	—	—		—	—	—	—	—	—	—	—	—	1
—	1	—	2	—	—	—	—	1	—	—	—	—		—	—	—	—	—	—	—	1	—	—
3	—	3	9	—	—	—	—	1	1	—	—	1		—	—	—	—	—	—	1	—	1	1
—	—	—	19	—	—	—	—	—	1	—	1	1		—	—	—	—	—	—	—	—	—	3
—	—	—	—																				
—	—	1	—																				
1	1	—	—																				
1	—	—	—																				
—	2	—	—																				

FRANDSENS TRYKKERI